Statistical analysis plan for the PEPTIC study (version 1)

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OUTCOME DEFINITIONS

Primary Outcome

The primary outcome is in-hospital all-cause mortality up to 90 days from the date of the index ICU admission. All patients discharged prior to 90 days and who survive the index hospital admission will be considered as alive at 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.

Secondary Outcomes

1. Clinically significant upper GI bleeding:

Defined as overt upper GI bleeding (e.g. haematemesis, melaena or frank blood in the nasogastric tube or upper GI endoscopy) developing as a complication in the ICU and accompanied by one or more of the following features within 24 hours of overt upper GI bleeding:

i. A spontaneous drop of systolic, diastolic, or mean arterial pressure ≥20 mmHg
ii. Initiation of a vasopressor or a 20% increase in ongoing vasopressor dose
iii. A decrease in haemoglobin of ≥20 g/L
iv. A transfusion of at least two units of packed red blood cells

2. *C. difficile* infection:

Defined as a patient who has a new *C. difficile* toxin or culture-positive stool sample collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission).

3. ICU length of stay

Defined as the time between ICU admission and ICU discharge for the index ICU admission (i.e. it excludes ICU readmission time and time spent in a second or subsequent ICU).

4. Hospital length of stay

Defined as the time between ICU admission and index hospital discharge (i.e. it excludes any time spent in hospital if readmitted).

Tertiary Outcome

1. Duration of mechanical ventilation:

Defined as the total hours of invasive mechanical ventilation during the index ICU admission. This includes any re-ventilation periods following initial weaning during the index ICU admission. For patients enrolled in the United Kingdom, duration of mechanical ventilation will be determined from the number of

calendar days (00:00 to 23:59) on which advanced respiratory support is received, because the United Kingdom database does not collect the number of hours of invasive mechanical ventilation. For patients who received advanced respiratory support on one calendar day, the total hours of invasive mechanical ventilation will be assumed to be 12. For patients who received advanced respiratory support on more than one calendar day, the total number of hours of invasive mechanical ventilation will be assumed to be 12 hours on the first day of advanced respiratory support, 12 hours on the last day of advanced respiratory support, and 24 hours on the intermediary days (i.e. the total number of hours of invasive ventilation will be calculated as the number of calendar days of advanced respiratory support minus one calendar day multiplied by 24 hours). If the total number of hours of invasive mechanical ventilation calculated by this method exceeds the total number of hours the patient spent in the ICU, the number of hours of mechanical ventilation will be truncated to equal the total hours the patient spend in the ICU. We anticipate that duration of mechanical ventilation will not be recorded in all participants / sites because collection of this variable was not mandatory in all sites at the time the study was conducted.

2. Ventilator-associated conditions

Defined as events where, after a period of stability or improvement on invasive mechanical ventilation of at least two days, a patient has at least one of the following indicators of worsening oxygenation:

i. An increase in daily minimum F_IO_2 of ≥0.20 over the daily minimum F_IO_2 in the baseline period of stability, sustained for at least two days;
ii. An increase in daily minimum positive end expiratory pressure (PEEP) values of at least three cmH_2O over the daily minimum PEEP in the baseline period, sustained for at least two days (daily minimum defined by lowest F_IO_2 or PEEP during a calendar day that is maintained for at least one hour)

The ventilator-associated conditions Outcome is available only for Canadian sites because data to derive this variable is not included in the registry databases from other countries.

STATISTICAL ANALYSES

Principles

Each patient will be included in the study only once so in the event that a patient is readmitted to hospital or the ICU after the initial qualifying ICU admission (index ICU admission), data that pertain to the second and any subsequent ICU or hospital admissions will not be included in the database. 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 the index ICU admission, regardless of treatment actually received. Descriptive statistics at ICU level will be presented by allocated treatment sequence, and patient characteristics will be summarised by allocated treatment sequence and observation period (see Table 1 and Tables S1 and S2 below).

Primary Outcome: in-hospital all-cause mortality up to 90 days from the date of the index ICU admission

Comparison of randomised treatment groups will use individual patient-level data and generalised estimating equations (GEE) with a logarithmic link function, an exchangeable working correlation matrix and robust standard errors using the ICU as the clustering unit. Because randomisation was performed in batches of ICUs, covariate adjustment for randomisation batch, the order of administration of the treatments, and batch-by-order interaction will be performed to allow for separate order/secular time effects occurring in each of the randomisation batches. Because the number of patients receiving each treatment will not be exactly equal within each ICU, the treatment effect will be partitioned into its within-ICU and between-ICU components by including the proportion of patients receiving treatment A in each ICU (which may be H_2RB or PPI) as a covariate together with the treatment group[1]. The within-ICU treatment effect estimate, not confounded by differences between ICUs and represented by the main effect of treatment arm in these models, will be reported. The effect of treatment comparisons will be presented as risk ratio and 95% confidence from the GEE analysis, and as a risk difference and 95% confidence interval obtained by marginalising/standardising of the risk ratio model[2] (Table 2). Should the risk ratio model fail to converge, GEE with Poisson outcomes, a logarithmic link, exchangeable working correlation and robust standard errors will be employed[3].

Analysis of Secondary and Tertiary Outcomes

Analysis of clinically significant upper GI bleeding, *C. difficile* infection, and ventilator associated conditions will follow the same approach as for the primary outcome, reporting risk ratios and 95% confidence intervals.

Time to discharge alive from index ICU and index hospital admission, and liberation from invasive mechanical ventilation will be summarised with medians and interquartile ranges obtained from cumulative incidence functions regarding mortality as a competing risk[4]. Treatment group comparisons will use Cox regression with covariate adjustment for the order of administration of treatments, and the batch-by-order interaction, with stratification by ICU, and robust standard errors clustered at ICU level (for any residual within-ICU correlation) to estimate cause-specific hazard ratios and confidence intervals, with patients dying prior to discharge (or extubation) censored at their time of death[4]. Assessment of the proportionality of hazards assumption in these models will be made using Schoenfeld residuals, with resultant covariate stratification or modelling of time-dependent treatment effects, where necessary. For the duration of invasive mechanical ventilation outcome, if the recorded duration of mechanical ventilation for a patient is within 48 hours of their duration of hospital stay resulting in death, then it will be assumed that such patients were extubated at that time with palliative intent and, hence, these patients' data will be censored at their time of extubation in the analyses.

Sensitivity analyses

Sensitivity to missing data in the primary and secondary outcomes

The main sensitivity analyses for the impact of missing primary and secondary outcomes will involve imputing outcomes under "worst-best" and "best-worst" case scenarios[5]. In the "worst-best" scenario for a binary outcome, a "worst" outcome event (e.g. in-hospital death within 90 days) is assigned to all patients missing the outcome in one treatment group, and a "best" outcome event (e.g. survival to hospital discharge within 90 days) is assigned to all patients missing the outcome in the other treatment group. The "best-worst" scenario is the exact opposite assignment of outcomes. For duration outcomes, the imputed values will be 0.001 days for the "best" case and a number larger than the maximum observed value for the "worst" case. Data with the best-worst and worst-best imputed outcomes will be analysed and the difference in the resulting two estimated treatment effects will indicate the range of uncertainty due to missing data for each outcome. If substantively different conclusions do not arise from these two analyses then no further missing data assessments will be performed for that outcome. If a substantively different conclusion does arise, then a more refined sensitivity analysis will employ a complete case log-binomial GEE (for binary) or Cox (for time-to-event) regression analysis adjusting for baseline covariates predictive of missingness of the specific outcome. These analyses use data from all patients who have complete outcome data, and are valid under the "covariate missing at random assumption" that missingness depends on the baseline covariates only and not on the value of the missing outcome itself or of other outcomes[6]. If more than 5% of the data for a primary or secondary outcome are missing[5], and when one outcome is missing for a patient but other outcomes are present, further sensitivity analyses will use multiple imputation methods using an imputation method that takes into account the outcomes that are available and the clustered data structure.

Additional analyses

Additional sensitivity analyses will (i) adjust for patient-level variables that exhibit imbalance across treatment groups within sequences, and (ii) exclude all patients transferred in from another ICU to the study ICU for the index admission.

Subgroup analyses

Planned subgroup analyses will assess heterogeneity of treatment effects for the primary and secondary outcomes across the following factors: (i) admitted to the ICU after cardiac surgery versus any other reason; (ii) emergency versus elective admissions, and (iii) region (sites from Ireland will be combined with UK sites and sites from Australia will be combined with New Zealand sites). These analyses will include interaction terms between treatment and subgroup in each of the respective regression models.

PROPOSED TABLES

Table 1: Baseline characteristics				
ICU Characteristics	**Sequence PPI/H2RB (number of ICUs=xxx)**		**Sequence H2RB/PPI (number of ICUs=xxx)**	
Region – n (%)				
ANZ	x (x)		x (x)	
Canada	x (x)		x (x)	
Ireland	x (x)		x (x)	
UK	x (x)		x (x)	
Number of beds	x±x		x±x	
Number of ICU admissions	x±x		x±x	
Type of ICU – n (%)	x (x)		x (x)	
Tertiary ICU (medical & surgical)	x (x)		x (x)	
Tertiary ICU (surgical)	x (x)		x (x)	
Tertiary ICU (medical)	x (x)		x (x)	
Non-tertiary ICU	x (x)		x (x)	
Patient Characteristics	**Period 1 PPI (n=xx)**	**Period 2 H_2RB (n=xx)**	**Period 1 H_2RB (n=xx)**	**Period 2 PPI (n=xx)**
Age – yr	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Co-morbid conditions – no. (%)				
Respiratory	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hepatic	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Immunosuppression	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Metastatic cancer	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Admission type – no. (%)				
Operative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Non-operative	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Source of admission to ICU – no. (%)				
Emergency department	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
From OT following elective surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
From OT following emergency surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Unknown	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
APACHE-II score*	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx
APACHE-III score†	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]	xx.x [xx.x-xx.x]
ANZ risk of death score (ANZ participants only)	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx
ICNARC risk of death score (UK participants only)	xx.x ± xx	xx.x ± xx	xx.x ± xx	xx.x ± xx

Plus-minus values will be expressed as mean ± SD
* Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.
† Scores on the APACHE III range from 0-299, with higher scores indicating more severe disease and a higher risk of death.
Abbreviations: ANZ: Australia & New Zealand; APACHE: Acute Physiology And Chronic Health Evaluation; ICNARC: Intensive Care National Audit & Research Centre; ICU: Intensive Care Unit; OT: operating theatre.

Table 2: Outcomes

	Default* PPI strategy (n=xxx)	Default* H_2RB strategy (n=xxx)	Estimate (95% CI)	P value
Primary outcome – no. (%)				
			Risk ratio	
In-hospital mortality	xx (xx.x)	xx (xx.x)	xx (xx to xx)	x.xx
			Risk difference	
			xx (xx to xx)	x.xx
Secondary outcomes – no. (%)				
Complications – no. (%)			**Risk ratio**	
Clinically significant upper GI bleeding	xx (xx.x)	xx (xx.x)	xx (xx to xx)	
Clostridium difficile infection	xx (xx.x)	xx (xx.x)	xx (xx to xx)	
Length of stay variables† (median, IQR)			**Hazard ratio‡**	
Days until discharged alive from ICU	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
Days until discharged alive from Hospital	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
Tertiary outcomes			**Hazard ratio‡**	
Hours until liberation alive from mechanical ventilation† -median, IQR	xx (xx-xx)	xx (xx-xx)	xx (xx to xx)	
			Risk ratio	
Ventilator associated conditions – no. § (%)	xx (xx.x)	xx (xx.x)	xx (xx to xx)	

* Two approaches to stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU were compared. One approach was to use PPIs as the default therapy when stress ulcer prophylaxis was prescribed and the other approach was to use H_2RBs as the default therapy when stress ulcer prophylaxis is prescribed. Clinicians decided whether or not individual patients would receive stress ulcer prophylaxis. When a clinician chose to prescribe stress ulcer prophylaxis, the default prescription of either PPI or H2RB was that allocated to the ICU for the current study treatment period. Irrespective of the treatment that was allocated to the ICU, the treating clinician could use either a PPI or an H_2RB for a particular patient at their discretion in situations where they considered that one or other treatment was preferable.
† Median and IQR reported with mortality regarded as a competing risk. Mortality rates by treatment group relevant to each variable will be reported in table footnotes.
‡ Hazard ratio will be estimated with mortality regarded as a competing risk. Accordingly, hazard ratios here will compare the treatment arms with reference to the chance of being being discharged alive or (liberated from mechanical ventilation alive) in the next short time interval (eg day) among patients currently alive and not discharge (or currently ventilated). For example, a hazard ratio of 1.10 means a 10% higher chance of being discharged alive (or liberated alive from mechanical ventilation) in the next day in one group than the other.
§ For participants from the eight Canadian ICUs.
Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; IQR: interquartile range; PPI: proton pump inhibitor

PROPOSED SUPPLEMENTAL TABLES

Table S1: Intensive Care Admission Diagnoses – ANZ, Irish, and Canadian ICUs

Diagnostic category	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)
Operative admission diagnosis – n (%)		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Gynaecological	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Metabolic	xxx (xx.x)	xxx (xx.x)
Musculoskeletal / skin	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Non-operative admission diagnosis – n (%)		
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Gynaecological	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)
Metabolic	xxx (xx.x)	xxx (xx.x)
Musculoskeletal / skin		
Neurological	xxx (xx.x)	xxx (xx.x)
Renal	xxx (xx.x)	xxx (xx.x)
Respiratory	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)

Abbreviations: ANZ: Australia and New Zealand; H_2RB: histamine-2 receptor blocker; ICUs: Intensive Care Units; PPI: proton pump inhibitor.

Table S2: Intensive Care Admission Diagnoses – UK ICUs

Diagnostic category	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)
Operative admission diagnosis – n (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Poisoning	xxx (xx.x)	xxx (xx.x)
Genito-urinary	xxx (xx.x)	xxx (xx.x)
Endocrine and metabolic	xxx (xx.x)	xxx (xx.x)
Haematological/Immunological	xxx (xx.x)	xxx (xx.x)
Musculoskeletal	xxx (xx.x)	xxx (xx.x)
Dermatological	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Non-operative admission diagnosis – n (%)		
Respiratory	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)
Poisoning	xxx (xx.x)	xxx (xx.x)
Genito-urinary	xxx (xx.x)	xxx (xx.x)
Endocrine and metabolic	xxx (xx.x)	xxx (xx.x)
Haematological/Immunological	xxx (xx.x)	xxx (xx.x)
Musculoskeletal	xxx (xx.x)	xxx (xx.x)
Dermatological	xxx (xx.x)	xxx (xx.x)
Trauma	xxx (xx.x)	xxx (xx.x)
Psychiatric	xxx (xx.x)	xxx (xx.x)

Abbreviations: UK: United Kingdom; H_2RB: histamine-2 receptor blocker; ICUs: Intensive Care Units; PPI: proton pump inhibitor

Table S3. Subgroup analyses – patient factors

	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)	Estimate (95% CI)	Interaction P value
In-hospital mortality within 90 days– no. (%)				
Admitted to ICU following cardiac surgery			Risk ratio	
Yes	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
No	xx (xx.x)	xx (xx.x)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Clinically significant upper GI bleeding – no (%)				
Admitted to ICU following cardiac surgery			Risk ratio	
Yes	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
No	xx (xx.x)	xx (xx.x)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Clostridium difficile infection – no (%)				
Admitted to ICU following cardiac surgery			Risk ratio	
Yes	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
No	xx (xx.x)	xx (xx.x)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index ICU admission – median, IQR*				
Admitted to ICU following cardiac surgery			Hazard ratio†	
Yes	xx (xx-xx)	xx (xx-xx)	x (x-x)	x.xx
No	xx (xx-xx)	xx (xx-xx)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index hospital admission– median, IQR*				
Admitted to ICU following cardiac surgery			Hazard ratio†	
Yes	xx (xx-xx)	xx (xx-xx)	x (x-x)	x.xx
No	xx (xx-xx)	xx (xx-xx)	x (x-x)	
Admission type				
Emergency	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Elective	xx (xx.x)	xx (xx.x)	x (x-x)	

* Median and IQR reported with mortality regarded as a competing risk. Mortality rates by treatment group relevant to each variable will be reported in table footnotes.
† Hazard ratio will be estimated with mortality regarded as a competing risk.
Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; IQR: interquartile range; PPI: proton pump inhibitor

Table S4. Subgroup analyses – ICU-level

	Default PPI strategy (n=xxx)	Default H_2RB strategy (n=xxx)	Estimate (95% CI)	Interaction P value
In-hospital mortality – no. (%)				
Country / Region			Risk ratio	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Clinically significant upper GI bleeding – no (%)				
Country / Region			Risk ratio	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Clostridium difficile infection – no (%)				
Country / Region			Risk ratio	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index ICU admission – median, IQR*				
Country / Region			Hazard ratio†	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	
Days until discharge alive from index hospital – median, IQR*				
Country / Region			Hazard ratio†	
ANZ	xx (xx.x)	xx (xx.x)	x (x-x)	x.xx
Canada	xx (xx.x)	xx (xx.x)	x (x-x)	
Ireland and UK	xx (xx.x)	xx (xx.x)	x (x-x)	

* Median and IQR reported with mortality regarded as a competing risk. Mortality rates by treatment group relevant to each variable will be reported in table footnotes.
† Hazard ratio will be estimated with mortality regarded as a competing risk.
Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; IQR: interquartile range; PPI: proton pump inhibitor

Table S5. Stress ulcer prophylaxis use in ICU #1*

	Default† PPI strategy (N=XXX)	Default† H_2RB strategy (N=XXX)
Monthly audit data – SUP use among ventilated adults		
Received PPI – n/N (%)	X/X (X)	X/X (X)
Received H_2RB – n/N (%)	X/X (X)	X/X (X)
Did not receive SUP – n/N (%)	X/X (X)	X/X (X)
Prescribed SUP to ventilated adults in each treatment period (mg)		
Ranitidine (enteral)	X	X
Ranitidine (intravenous)	X	X
Esomeprazole (all routes)	X	X
Omeprazole (all routes)	X	X
Pantoprazole (all routes)	X	X
SUP dispensed from the pharmacy in each treatment period (mg)		
Ranitidine (enteral)	X	X
Ranitidine (intravenous)	X	X
Esomeprazole (all routes)	X	X
Omeprazole (all routes)	X	X
Pantoprazole (all routes)	X	X

Abbreviations: IV: intravenous; SUP: stress ulcer

* An equivalent table will be presented with stress ulcer prophylaxis data for each study ICU

† Two approaches to stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU were compared. One approach was to use PPIs as the default therapy when stress ulcer prophylaxis was prescribed and the other approach was to use H_2RBs as the default therapy when stress ulcer prophylaxis is prescribed. Clinicians decided whether or not individual patients would receive stress ulcer prophylaxis. When a clinician chose to prescribe stress ulcer prophylaxis, the default prescription of either PPI or H2RB was that allocated to the ICU for the current study treatment period. Irrespective of the treatment that was allocated to the ICU, the treating clinician could use either a PPI or an H_2RB for a particular patient at their discretion in situations where they considered that one or other treatment was preferable.

Abbreviations: CI: Confidence Interval; H_2RB: histamine-2 receptor blocker; ICU: intensive care unit; PPI: proton pump inhibitor

PROPOSED FIGURES:

Figure 1: Participant flow diagram

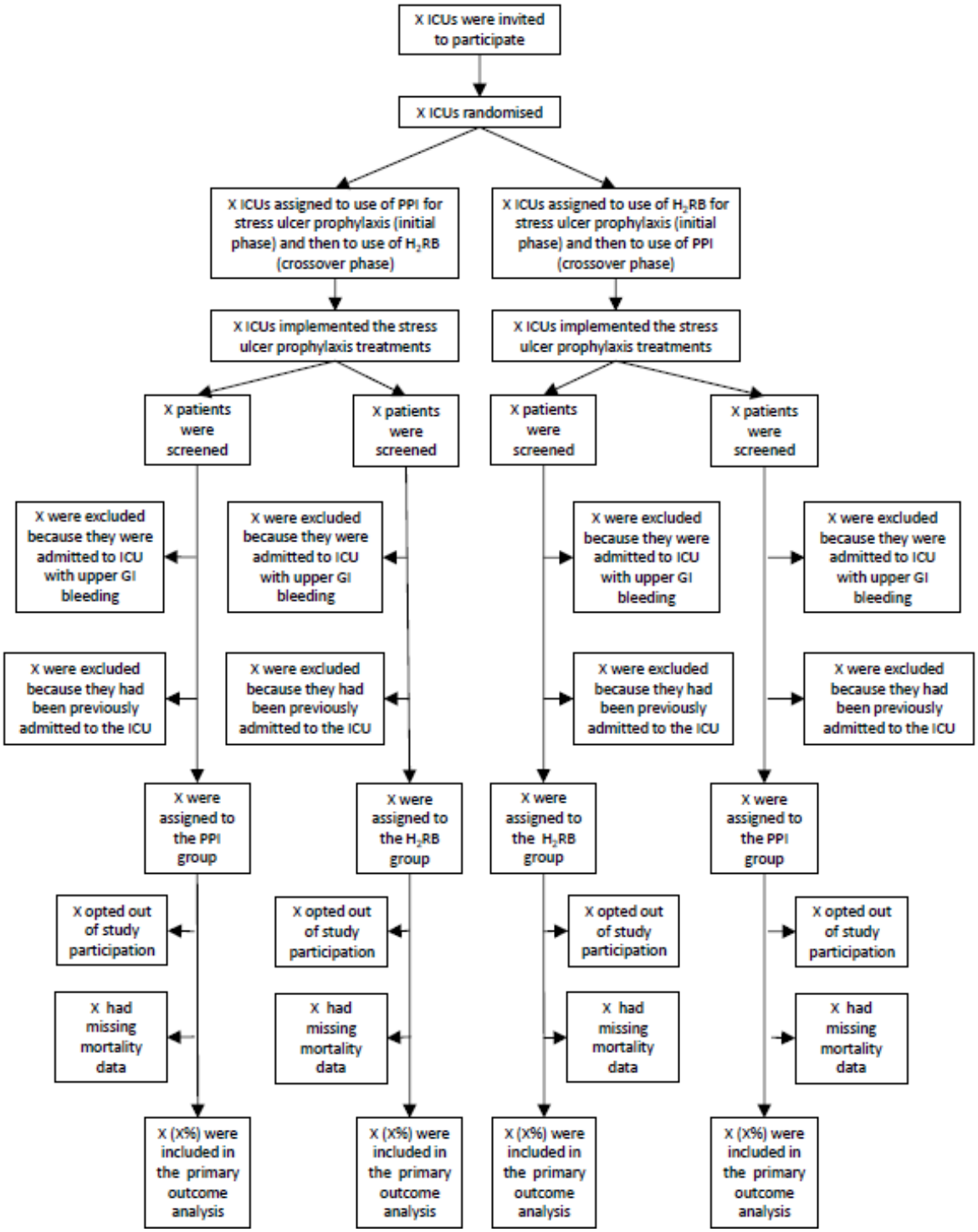

Figure 2: Estimated exposure to study treatment by sequence and treatment period

An example of the proposed lay-out is shown below with mock data for two ICUs:

Sequence PPI/H_2RB (number of ICUs=XX)			Sequence H_2RB/PPI (number of ICUs=XX)		
ICU	Period 1 PPI (n=XXXX)	Period 2 H_2RB (n=XXXX)	ICU	Period 1 H_2RB (n=XXXX)	Period 2 PPI (n=XXXX)
1			2		

Additional lines will be added for each of the study ICUs. Each Silhouette will represent 25 patients. The proportion of mechanically ventilated adults who received PPI (red), H2RB (blue), both PPI and H2RB (purple), and neither (grey) will be based on monthly audits that were performed during the conduct of the study at each site. These proportions will be multiplied by the number of patients admitted to each site in each period, divided by 25, and rounded to the nearest whole number to calculate the number of silhouettes that will be displayed. If there are fewer than 25 patients, no silhouette will be displayed.

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