Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med. DOI: 10.1056/NEJMoa1714919

This supplement contains the following items

1. Original protocol (October 2015), page 3-93
2. Final protocol (August 2017), page 94-195
3. Summary of changes to protocol, page 196
4. Original/final statistical analysis plan (no amendments to original version) (May 2017), page 197-209

Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial

<u>Original</u> protocol, version 3.0, October 20th, 2015

Applicable protocol registration numbers:
EudraCT number: 2015-000318-24
ClinicalTrials.gov Identifier: NCT02467621

In drafting of present protocol Copenhagen Trial Unit's Standard Operating Procedures were used

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Abstract

Background: Critically ill patients in the intensive care unit (ICU) are at risk of stress related gastrointestinal (GI) bleeding, and stress ulcer prophylaxis (SUP) is recommended. However, the evidence on SUP is of low quantity and quality, and studies have shown that proton pump inhibitors (PPI) may increase the risk of a number of serious adverse events.

Objectives: To assess the benefits and harms of SUP with PPI in adult, critically ill patients in the ICU.

Design: An investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of SUP with PPI versus placebo.

Inclusion and exclusion criteria: Inclusion criteria: Adult patients admitted to the ICU with one or more of the following acute conditions: shock, renal replacement therapy, mechanical ventilation expected to last > 24 hours, any kind of coagulopathy, treatment with anticoagulant drugs or liver disease. Exclusion criteria: contraindications to PPI, daily treatment with PPI and/or histamine-2-receptor antagonist, GI bleeding of any origin or known peptic ulcer during current hospital admission, organ transplant, withdrawal from active therapy or brain death, positive urine human chorionic gonadotropin (hCG) or plasma hCG or consent according to national regulations not obtainable.

Intervention: Experimental intervention is intravenous pantoprazole 40 mg daily. Control intervention is matching placebo (saline).

Outcomes: Primary outcome: Mortality 90 days after randomisation. Secondary outcomes: proportion of patients with clinically important GI bleeding, pneumonia, *Clostridium difficile* infection and myocardial ischemia, proportion of patients with clinically important GI bleeding, proportion of patients with pneumonia or *clostridium difficile infections*, 1 year mortality post-randomisation, days alive without organ support in the 90-day period, serious adverse reactions and a health economic analysis

Trial size: 2 x 1675 patients are required to show a 20% relative risk reduction or increase (5% absolute risk reduction or increase) in the primary outcome measure, assuming a baseline 90-day mortality of 25% (α=0.05 (two-sided), and β=0.1)

Time schedule:

2014 – November 2015: Governance approval applications, education of trial sites, other preparations

December 2015: First Danish patient enrolled

February 2015: Commencement of inclusion in other countries

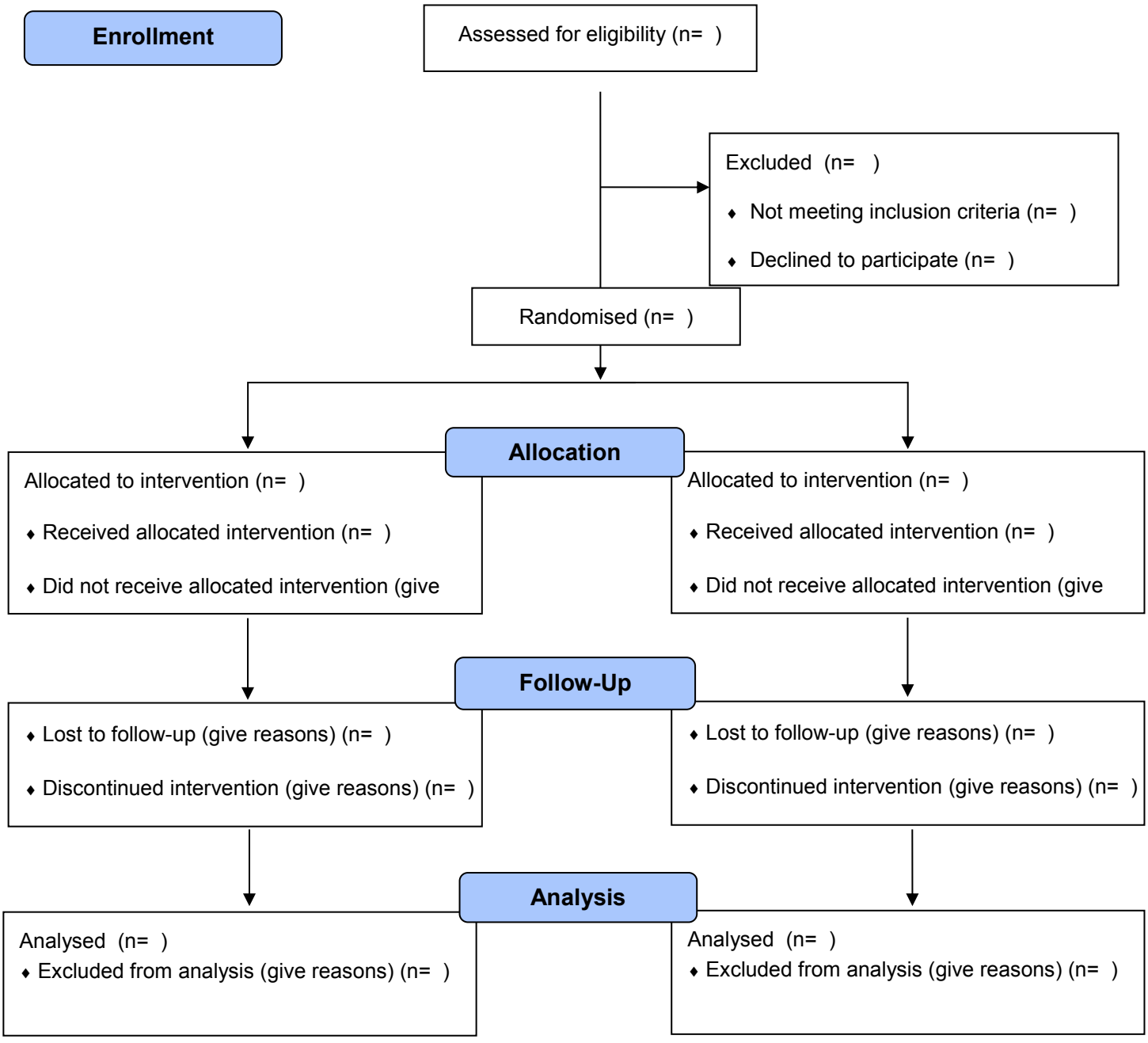
November 2017: Last patient enrolled

January 2018: Follow-up completed

May 2018: Data analysis and submission for publication

Trial flow chart

The flowchart (n=) will be filled in during or at the end of the trial.



Administrative information

The research programme organisation is attached in *appendix* 1

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- Switzerland
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List of abbreviations

AE	Adverse events
AIDS	Acquired Immune Deficiency Syndrome
AR	Adverse reactions
ARR	Absolute risk reduction
CDI	*Clostridium difficile* infection
CI	Confidence interval
CRIC	Centre for Research in Intensive Care
CRO	Contract research organisation
CT	Computed Tomography
CTSM	Clinical Trial Supply Management
DMSC	Data Monitoring and Safety Committee
eCRF	Electronic case report form
FiO2	Fractional inspired oxygen
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GI	Gastrointestinal
H2RA	Histamine-2-receptor antagonist
hCG	Human Chorionic Gonadotropin
ICU	Intensive care unit
INR	International normalized ratio
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MR	Magnetic Resonance
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PaO2	Partial pressure of oxygen in arterial blood
PPI	Proton pump inhibitor
PT	Prothrombin time
RCT	Randomised clinical trial

RRI	Relative risk increase
RRR	Relative risk reduction
SAE	Serious adverse event
SAPS	Simplified Acute Physiology Score
SAR	Serious adverse reaction
SC	Steering Committee
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
SUP	Stress ulcer prophylaxis
SUSAR	Severe unexpected serious adverse reaction
TSA	Trial sequential analysis

1. Introduction and background

1.1 The patient population

Critically ill patients are at risk of stress-related gastrointestinal (GI) mucosal damage, which can progress to ulceration and GI bleeding [1]. Endoscopic studies have shown that gastric erosions are present in up to 90% of patients by the third day in the intensive care unit (ICU) [2, 3]. These lesions are in the vast majority of patients superficial and asymptomatic, but can progress and result in overt and clinically important bleeding [4]. Clinical important bleeding in the ICU is a serious condition, with an estimated 1-4 times increased risk of mortality and is associated with an excess length of ICU stay of 4-8 days [1].

Determining the incidence of GI bleeding in critically ill patients in the ICU is complicated by varying definitions of the outcome, difficulties in measuring the outcome, and different case mix. In randomised clinical trials (RCTs) and observational studies, the reported incidence of stress related GI bleeding among ICU patients ranges from 0.6-6.0% [1, 5–9]. Studies may have incorrectly included bleedings not related to stress ulcers e.g. oesophageal varices and ulcers already present upon ICU admission, e.g. undiagnosed peptic ulcers. In a prospective study by Cook *at al*. causes of haemorrhage were identified by endoscopy. Stress ulceration was defined as the sole source of bleeding in 14 of 30 patients [10]. Accordingly, sources of GI bleeding not prevented by stress ulcer prophylaxis (SUP) are frequent and the incidence of stress related ulcers may be lower than reported. Furthermore, diagnostics and treatment of critically ill patients in the ICU have improved considerably during the last decades [11, 12] and the incidence of stress ulcerations in critically ill patients may have changed.

1.2 Current treatment

Clinical trials have suggested a reduction in frequency of GI bleeding among ICU patients receiving SUP compared with patients receiving placebo or no prophylaxis [3, 13–19]. Based on this research conducted 20 years ago, SUP is recommended in international guidelines [20–23] and regarded as standard of care in the ICU. In a recent international unit evaluation 96 out of 97 units used SUP on a regular basis [24] and proton pump inhibitor (PPI) was used as first-line therapy in 66% of the participating ICUs [24].

The available PPIs are considered equally effective in the following comparative doses [25–29]:

Esomeprazole	10 mg

Lanzoprazole	15 mg
Omeprazole	10 mg
Pantoprazole	20 mg
Rabeprazole	10 mg

In 2014 Maclaren *et al*. published a retrospective cohort study with data from the Premier Perspective Database [30]. Patients aged 18 years or older requiring invasive mechanical ventilation and receiving either Histamine-2-receptor antagonist (H2RA) or PPI were scrutinized. Some 35,312 patients were included and among other findings the authors found that pantoprazole was the most frequently used PPI. This finding was confirmed in a cohort study from 2014, where pantoprazole was prescribed to 32% of patients treated with acid suppressants in the ICU [9].

1.3 Trial interventions

Because of the increased mortality and morbidity of ICU patients with clinically important GI bleeding, it is theoretically possible that PPIs reduce the risk of GI bleeding and hence the risk of death. However, research has not been able to confirm this and a 2014 observational study comprising more than 1,000 patients concludes that part of the increased mortality is explained by confounding [9]. A recent systematic review with meta-analysis and trial sequential analysis (TSA) assessed randomised trials comparing PPI or H2RA to placebo or no prophylaxis [31]. The review was conducted according to the Cochrane Handbook for Systematic Reviews [32] and included 20 trials with high risk of bias. The review results showed no significant difference between SUP and placebo/no prophylaxis on mortality and the TSA could exclude a 20% relative risk reduction or increase in mortality by using PPI or H2RA. Another meta-analysis from 2010 came to the same conclusion. Mortality was reported in 14 of the analysed trials and no significant reduction in mortality was found (OR 1.03, 95% CI 0.78-1.37; p=0.82).

Three RCTs have been conducted comparing PPI to placebo [33–35], but all had low sample size (n=169 [33], n=287 [34], and n=41 [35]) and neither of them were powered to show statistically significant differences in clinically relevant outcomes. The 2014 meta-analysis

comprised two of the trials (one was published after the meta-analysis) and concluded that the trials had a high risk of bias, and there were no differences in GI bleeding, pneumonia and mortality when comparing PPI to placebo.

PPI may reduce the risk of GI bleeding, but studies have indicated that they may also increase the risk of pneumonia, *Clostridium difficile* infection (CDI), acute myocardial ischemia, rhabdomyolysis, hypomagnesaemia and hypocalcaemia, and all of these conditions may increase the risk of death [36–39].

PPI versus H2RA

In recent years PPI has been considered the drug of choice in the management of most acid-related GI disorders [40]. The superior efficacy of PPIs over H2RAs has been demonstrated in various GI disorders, including peptic ulcer disease, gastroesophageal reflux disease and GI damage caused by non-steroidal anti-inflammatory drugs (NSAIDs) [40]. Randomised trials and meta-analyses have aimed to evaluate PPI compared to H2RA as SUP in the ICU. A recent published meta-analysis by Alhazzani et al. (14 trials, 1720 patients) compared PPI and H2RA [41]. The authors found that PPI was more efficient in reducing clinically important and overt GI bleeding, but no differences were shown regarding mortality, length of stay or pneumonia [41]. According to the authors the results were limited by sparse data, a difference between lower and higher quality trials, trial methodology and possible publication bias. Another systematic review and meta-analysis conducted in 2010 compared PPI and H2RA [42]. The study comprised seven RCTs and 936 ICU patients. The analysis did not find differences in rates of clinically important GI bleeding, pneumonia or death. Limitations of the review include limited number of patients, significant statistical heterogeneity, and risk of publication bias.

Clinical data on the control intervention

As described in previous section, studies have indicated that PPI is superior to H2RA to prevent clinically important and overt GI bleeding, but there is still a lack of quantitative and qualitative evidence for PPI being superior to placebo. Before comparing different SUP agents we need firm evidence of SUP being superior to placebo.

1.4 Adverse effects of PPI

Nosocomial pneumonia

Nosocomial infections are a significant in-hospital burden, and pneumonia is the most common nosocomial infection in the ICU, affecting 10–20% of patients receiving mechanical

ventilation for more than 48 hours [43]. It has been suggested that SUP agents may increase the frequency of nosocomial pneumonia and trials have investigated the incidence of pneumonia in patients treated with SUP compared to placebo/no prophylaxis [6, 17, 33, 34, 37, 44–46]. In 2004 Kantorova *et al.* found an insignificant difference in the incidence of pneumonia in patients treated with PPI/H2RA compared to placebo (n=287, 10%/9% vs. 7%). No meta-analysis of randomised trials have shown a statistically significant increased risk of nosocomial pneumonia when using SUP compared to placebo/no prophylaxis [31, 47].

Clostridium difficile infection

In recent years, concern has been raised that PPI increases the risk of CDI because host immunity is compromised by higher gastric pH [38, 48]. No randomised trials of SUP have reported the incidence of CDI in an ICU setting, but a recently published cohort study in adult critically ill patients requiring mechanical ventilation (n=35,312) found a 2-4 times increased risk of CDI in patients receiving PPIs compared to H2RAs [30]. Studies conducted outside the ICU demonstrate similar findings. In 2007 Leonard *et al.* found a significantly increased risk of CDI in non-ICU patients receiving H2RA or PPI, as compared to placebo [49] and a meta-analysis pooling 39 observational studies showed a significant association between PPI users and risk of developing CDI (OR 1.74, 95% CI 1.16-5.44) compared with non-users [50].

Acute myocardial ischemia

An association between use of PPIs and increased risk of cardiovascular events in patients receiving clopidogrel have been suggested [47, 51]. It may be that PPIs reduce the anti-platelet effects of clopidogrel, by interaction with the Cytochrome P450 enzyme complex in the liver [51]. In a case-control study of 18,130 clopidogrel users, use of co-existing PPI was associated with an increased risk of cardiovascular complications [51]. However, in the only RCT published, no cardiovascular interaction between clopidogrel and PPI was observed in non-ICU patients [42]. A cohort-study including 56,406 patients hospitalized for myocardial infarction or stroke, found an association between treatment with PPI and adverse cardiovascular outcomes after discharge regardless of treatment with clopidogrel [52].

In conclusion, valid evidence on the use of SUP in the ICU is lacking. Moreover, there is increasing concern about side-effects of SUP, in particular PPIs, but the data on side-effects are of very low quality.

1.5 Risks and benefits

Since PPI is a well-established drug and thousands of patients are treated with it every day, there will be no additional risk to patients receiving PPI. The risk will be limited to the known adverse reactions, including intolerance, abdominal pain and headache (*appendix* 2)
From the available evidence we do not know whether there will be a higher risk of GI bleeding, pneumonia, CDI, cardiovascular events or mortality in the PPI or placebo groups [31].

1.6 Ethical justification and trial rationale

As described in former sections, there is no firm evidence from systematic reviews of RCTs or single RCTs on the potential benefit or harm of PPIs in adult patients in the ICU. On the other hand, SUP is recommended in international guidelines [20–22], is regarded as standard of care and surveys have confirmed that PPI is already part of the treatment in ICUs worldwide. Since it is a widespread and currently used intervention [24], the patients assigned to the PPI group, will not be exposed to additional risk when enrolled in the trial. Any patient with known peptic ulcer or GI bleeding will be excluded and treated according to usual care. If a randomised patient develops upper GI bleeding and the clinician finds indication for treatment with PPI or H2RA, the trial intervention will be discontinued and the patient will be treated according to usual care. Therefore, patients in the control group will, presumably, also not be exposed to any additional risks.
Stress ulceration is a condition often seen in critically ill patients in the ICU. The majority of patients will be temporarily incompetent because of severe illness or as a consequence of the treatment (sedation). We cannot perform the trial randomising competent patients, because less sick (and thus competent) patients do not suffer from stress ulcers. Patients requiring acute treatment in the ICU e.g. mechanical ventilation are in an acute life-threatening condition and it would expose the patient to great risk not to initiate the necessary treatment in order to get informed consent. To make clinical trials with the goal of improving the outcome for ICU patients at risk of stress related GI bleeding, it is necessary to randomise and enrol patients before obtaining informed consent from the patient. Consent will be obtained according to national law, which in Denmark is by proxy (consent before randomisation by 2 doctors followed by next-of-kin and general practitioner/regional medical officer by health as soon as possible). The consenting party will be provided with written and oral information about the trial, so he/she is able to make an informed decision about participation in the trial. Written information and the consent form will be subjected to review and approval by the ethical

committee system according to national law in all participating countries. The consenting party can at any time, without further explanation, withdraw consent and data will be deleted if demanded.
The process leading to the achievement of consent may differ in the participating countries, but will be described and be in compliance with all applicable regulations in the country.
No biological material will be collected for the trial, thus no bio-bank will be formed.

1.6.1 Outcome considerations

It has been estimated that 39% of the patients receiving SUP in the ICU are discharged from the hospital with SUP without an obvious indication for continuation of therapy [53]. Besides the side effects described in former sections, long-term treatment with PPI is associated with several side effects e.g. an increased risk of fractures, hypomagnesaemia and rhabdomyolysis [36, 39], which may all have the potential to increase mortality. Assessing mortality as the primary outcome would give the opportunity to weigh the totality of benefits and harms of PPI. Furthermore the rationale for choice of outcomes is:

1. Mortality has not been the primary outcome of previous trials and we are sceptical that they got reliable information on mortality other than short term mortality (ICU/hospital) [31]
2. Nearly all previous trials assessing PPI or H2RA as SUP have had high risk of bias [31]. We know that high risk of bias trials tend to overestimate benefit and underestimate harm [54]. Accordingly, previous trial results might be biased and even though they seem to find a neutral effect on mortality this may be a biased estimate actually concealing excess mortality in the SUP groups
3. A meta-analysis of the previous trials did not reach a realistic information size so even neutral estimates may be misleading [31].
4. As a consequence of the 6S trial [55], where we found that bleeding was associated with death and that death where partly mediated by bleeding (and renal insufficiency), it appears odd that there should be a clinically significant reduction on GI bleeding (if PPI do prevent GI bleeding) without any effect on mortality [56].
5. A composite outcome of GI bleeding, pneumonia, CDI and acute myocardial ischemia seems valid to assess as well and will be a secondary outcome. The recommendation for using composite outcomes is reporting of the individual components as well, which will be done in a supplement to the primary publication.

Because of this and the potential to improve treatment of critically ill patients, the research question is in the public's interest. The design of the trial will minimise the risk of systematic errors and the trial will provide information on beneficial and/or harmful effects of using PPI as SUP.

1.6.2 Sample size considerations

It is difficult to produce reliable sample size estimations according to anticipated effects on GI bleeding because we have no reliable control groups due to the widespread use of PPI [57] and previous trials are in fact very old. As a consequence it has been necessary to calculate sample size estimations given that something may change if we stop/avoid PPI until GI bleeding actually happens (see *appendix* 11). The addressed intervention effect of 20% RRR or RRI on the primary outcome may seem high, but in a population with septic shock or in e.g. patients after cardiac arrest a 20% hazard ratio reduction corresponds to 1 months of extra median survival in patients with a median survival of approximately 5 months. So after all, a 20% RRR or RRI may not be as huge as could be anticipated, when it only results in a modestly longer survival in these patients. The power for even major effects on each of the possible side effects (pneumonia, CDI and acute myocardial ischemia) are small, but it will still be a large contribution to our knowledge on these outcomes that may seriously question, overthrow or confirm what we know so far. Furthermore, 3,350 patients included in one trial would be a huge contribution to the evidence, more than doubling the number of randomised patients and providing trial results with low risk of bias on mortality and serious adverse events.

No single trial, however big or well done, gives the final answer, and the SUP-ICU trial will not be an exception. However, the results will inform clinicians, guideline committee members and policy-makers on the use of PPI in the ICUs, as well as establish more (reliable) trust in PPI. Should we find 10-20% relative risk increase in mortality this will certainly trigger a new wave of trials on PPI or SUP in general and even though our trial may not be conclusive it may eventually lead to conclusions.

1.7 Trial conduct

The trial will be conducted in compliance with a published trial protocol, the Helsinki Declaration in its latest version [58], the good clinical practice (GCP) guidelines [59], and national laws in the participating countries. The protocol will be registered on

www.clinicaltrials.gov and at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) before trial start. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible. Enrolment will start after approval by the ethical committees, medicines agencies, data protection agencies and health authorities in the participating countries. A manuscript with main points of the protocol including description of design, rationale and analysis plan will be submitted to a journal in English language.

2. Trial objectives and purpose

To assess the benefits and harms of PPI (pantoprazole) in adult, critically ill patients in the ICU.

3. Trial design

3.1 Trial design

An investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of pantoprazole versus placebo.

3.2 Randomisation

Patients will be screened for enrolment at admission to the ICU (see section 3.5). This will be ensured through implementation of trial methodology at trial sites.
1:1 randomisation will be centralised and web-based randomisation according to the computer-generated allocation sequence list, stratification variables (site and active hematologic cancer), and varying block size. The allocation sequence list will be unknown to the investigators to allow immediate and concealed allocation to intervention with pantoprazole or placebo. Each patient will be allocated a unique patient-screening number.

3.3 Blinding

Pantoprazole is preserved as a powder in a glass vial and needs to be dissolved in 10 ml of isotonic saline. The powder is momentarily dissolved with no need of shaking the vial. The solution is colourless and cannot be distinguished from saline. When the glass vial is masked,

it is not possible to determine whether the vial contains powder or is empty. The placebo will be an empty vial. Saline (10 ml) will be added to the empty vial in the same way as for the experimental intervention.
The blinding of the trial medication will be a white label covering the whole vial including the bottom and the neck. The label will contain the required information of the trial drugs. The top of the placebo vial will be identical with the vial of the active drug.
The allocated trial medication will be blinded to the clinical staff caring for the patient, to the patient, investigators, outcome assessors, and the data manager. The statistical analysis of the trial will be blinded with the intervention groups coded as, e.g., X and Y. Based on this blinded analysis two conclusions will be drawn: one assuming X is the experimental group and Y is the control group, and one conclusion assuming the opposite. Two abstracts will be written and accepted by the author group. After this, the blinding will be broken.

The members of the Data Monitoring and Safety Committee (DMSC) will remain blinded unless 1) they request otherwise or 2) one of the two interim analyses has provided strong indications of one intervention being beneficial or harmful (a charter for the independent DMSC is attached in *appendix* 3).

3.3.1 Unblinding

3.3.1.1 An individual
The intervention may be unblinded for individual patients if deemed necessary by the clinician or investigator for the treatment and safety of the patient.
In case of a suspected unexpected serious adverse reaction (SUSAR) the sponsor (or delegated party) shall break the blinding in order to judge the ‘expectedness’ and therefore the occurrence of a SUSAR (according to the summary of product characteristics), and report it to the authorities accordingly. See section 8 for more information.

3.3.1.2 Procedure
If the intervention for an individual patient needs to be unblinded during the trial, the treating physician shall contact Copenhagen Trial Unit (CTU), who will reveal the allocated trial intervention (pantoprazole or placebo). This can be done by telephone at all hours, any day of the week. If the investigator needs immediate unblinding of the trial medication, this can be done by removing the white label covering the glass vial.

3.5 Participant timeline

We will strive to enrol patients as soon as they fulfil the inclusion criteria. Patients will be allocated to either intravenous pantoprazole or placebo once daily and will continue the allocated intervention until death in the ICU or discharge from the ICU with a maximum of 90 days after randomisation.

If the patient is readmitted to the ICU within 90 days after randomisation the patient should continue the allocated treatment.

4. Selection of participants

All patients referred to a participating clinical trial site will be considered for participation. Patients will be eligible, if they fulfil all of the inclusion criteria and none of the exclusion criteria listed below (see also *appendix* 4)

4.1 Inclusion criteria

- Acute admission to the ICU **AND**
- Aged ≥ 18 years **AND**
- One or more of the following risk factors:
    - Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70 mmHg or lactate > 4 mmol/l)
    - Acute or chronic intermittent or continuous renal replacement therapy
    - Invasive mechanically ventilation which is expected to last > 24 hours. When in doubt of the forecast, the patient should be enrolled
    - Coagulopathy (platelets < 50 x 10^9/l or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds) documented within the last 24 hours
    - Ongoing treatment with anticoagulant drugs (prophylaxis doses excluded)
    - History of coagulopathy (platelets < 50 x 10^9/l or INR > 1.5 or PT > 20 seconds within 6 months prior to hospital admission
    - History of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history)

4.2 Exclusion criteria

- Contraindications to PPI
- Ongoing treatment with PPI and/or H2RA on a daily basis
- GI bleeding of any origin during current hospital admission
- Diagnosed with peptic ulcer during current hospital admission
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death
- Fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma-hCG
- Consent according to national regulations not obtainable

4.3 Participant discontinuation and withdrawal

4.3.1 Discontinuation and withdrawal at the choice of the participant

The procedure of handling withdrawal of consent from a patient will follow national regulations and will be described by each participating country.

The Danish procedure:
A patient, who no longer wishes to participate in the trial, can withdraw his/her consent at any time without need of further explanation, and without consequences for further treatment. Patients may be withdrawn from the trial at any time if consent is withdrawn by the person(s), who has given proxy-consent.
In order to limit the amount of missing data we plan to collect as much data from each patient as possible. Therefore, if possible, the investigator will ask the patient which aspects of the trial, he/she wishes to withdraw from:

- receiving the trial intervention only (allowing for all data registration and follow-up)

OR

- receiving the trial intervention AND further registration of daily data and/or follow-up

Only the patient can demand deletion of already registered data and only if the patient did not consent previously. If so, data will be deleted and a new patient will be randomised to obtain the full sample size.

4.3.2 Discontinuation and withdrawal at the choice of the investigator

A patient can be discontinued from the trial intervention by the investigator at any time, if:

- the patient experiences intolerable adverse reactions suspected to be related to the trial intervention

AND/OR

- the patient develops upper GI bleeding or another condition where the clinician finds indication for treatment with PPI or H2RA. The intervention will be stopped and the patient will receive relevant treatment.

In these cases, the collection of data will continue and the follow-up will be conducted. The patient will remain in the intention-to-treat population if the allocated trial intervention has been given.

If an ineligible patient is randomised by mistake and the trial intervention has not been given, data will be deleted (logged as a flawed randomisation) and a new patient will be randomised [60]. If the intervention has been given, the patient will continue in the trial and in the intention-to-treat population.

If the patient experiences a serious adverse reaction (SAR) or a suspected unexpected serious adverse reaction (SUSAR) the trial intervention will be stopped; data registration will continue (see section 8).

Patients who are transferred to another ICU will be regarded as discharged from the ICU unless the new ICU is an active SUP-ICU trial site. In any case, patients transferred to another ICU will be followed up for the primary outcome measure and as many of the secondary outcome measures as possible.

5. Selection and trial sites and personnel

5.1 Trial sites and setting

Trial sites will be ICUs [61] in Europe. Trial sites are listed in the section 'Administrative information'. This section will be updated during the trial.

5.2 Trial personnel

All clinicians caring for patients in participating ICUs will be eligible to screen patients and perform the interventions.

All participating ICUs will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for questions.

6. Trial interventions

6.1 Experimental intervention

To ensure systemic uptake of pantoprazole all patients randomised to the experimental group will be given intravenous pantoprazole 40 mg upon randomisation and hereafter once daily. The intervention period will be from randomisation until discharge from the ICU or death in the ICU. If the patient is readmitted, the allocated intervention should be continued until final discharge from the ICU or the end of the 90-day trial period.

6.2 Control intervention

The control intervention will be placebo as described in section 3.3.
The intervention period will be identical to the intervention period of the experimental intervention.

6.3 Co-interventions

All patients in this trial will be offered co-interventions if indicated. Evidence regarding the use of sucralfate and antacids are weak [62] and we do not recommend the use of these drugs.

The registered co-interventions will be:

- any kind of mechanical ventilation (y/n) (daily)
- continuous treatment with vasopressor/inotropes (y/n) (daily)
- renal replacement therapy (y/n) (daily)
- number of units of red blood cells (daily)
- enteral nutrition (y/n) (daily)

ICU treatment and management in general will be at the discretion of the treating clinicians.

6.4 Concomitant interventions

PPI or H2RA cannot be prescribed as prophylaxis in the ICU during the intervention period. If the patient develops GI bleeding or another condition where treatment with one of the drugs is

indicted, the patient will be withdrawn from trial intervention and receive relevant treatment. Data collection will continue. If an included patient receives open-label PPI/H2RA (e.g. prescribed as prophylaxis) it will be considered a major protocol violation. This will be registered and the allocated trial intervention and data collection will be continued.

Previously randomised patients readmitted to the ICU:

- If the clinician finds indication to continue the PPI or H2RA prescribed in the ward, the trial medication will not be resumed, but data collection will continue
- If the clinician does not find indication to continue the PPI or H2RA prescribed in the ward, the drug will be discontinued and the allocated trial medication will be resumed

All other interventions will be allowed since they are expected to be distributed evenly in the two groups.

6.5 Intervention accountability

Pantoprazole for intravenous injection will be bought and delivered from Actavis to the Hospital Pharmacy of the Capital Region of Denmark. The pantoprazole will be part of the regular production and hence not made especially for the SUP-ICU trial. The Hospital Pharmacy will send it directly to Nomeco. Pharma-Skan ApS will produce the sterile empty vials used for placebo. The production will follow all regulations and according to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). The vials will be delivered to Nomeco CTSM who will be responsible for storage, blinding, packaging and distribution of vials with pantoprazole 40 mg and empty vials (placebo) to national and international trial sites. All services will be performed by qualified and trained personnel and according to GMP and GDP

A computer program (from CTU) will generate a coding list with numbers for the vials**.** At randomisation, the computer program will allocate vials from the specific trial site to the patient. Nomeco CTSM will be responsible for having a sufficient number of vials to be allocated to patients enrolled at each trial site. At each trial site, trial products will be stored in a secure place. Combined with the unique packaging and labelling number this will ensure that trial medications will not be mixed up with other medications. Used and unused products will be registered.

7. Outcomes

All outcomes are defined in *appendix* 4.

7.1 Primary outcome

90-day mortality post-randomisation

7.2 Secondary outcomes

- Proportion of patients with one or more of the following adverse events: clinically important GI bleeding, pneumonia, CDI, or acute myocardial ischemia in the ICU
- Proportion of patients with clinically important GI bleeding in the ICU
- Proportion of patients with one or more infectious adverse events (pneumonia or CDI) in the ICU
- 1-year "landmark" mortality post-randomisation
- Days alive without the use of mechanical ventilation, renal replacement therapy or circulatory support in the 90-day period
- Number of SARs as defined in a*ppendix* 4
- A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-benefit vs cost-minimisation analyses)

The specific elements of the composite outcomes will be reported in supplementary material to the primary publication.

7.3 Exploratory outcomes

No exploratory outcomes or sub-studies are planned. However, sub-studies will be encouraged as long as they don't hamper the completion of the main protocol and can be conducted after approval of the protocol by the Steering Committee (SC).

8. Safety

8.1 Definitions

Adverse event (AE): any undesirable medical event occurring to a patient during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a patient during a clinical trial. Adverse reactions are specified in the product characteristics of pantoprazole (see *appendix* 2 and 5)

Serious adverse event (SAE): any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity.

Serious adverse reaction (SAR): any adverse reaction (as defined above) that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity.

Suspected unexpected serious adverse reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected. SUSARs will be defined as serious reactions not described in the summaries of product characteristics for pantoprazole**.**

8.2 Risk and safety issues in the current trial

Pantoprazole is well tolerated and most adverse reactions have been mild and transient showing no consistent relationship with treatment. Approximately 5% of patients can be expected to experience adverse drug reactions. The most commonly reported are diarrhoea and headache, both occurring in approximately 1% of patients. Because of intravenous administration, there will be a risk of phlebitis in both groups.
In *appendix* 2 all adverse reactions for pantoprazole are listed.
Apart from the risk of phlebitis, there is no risk of adverse reactions to the placebo (10 ml of isotonic saline).
See Summary of Product Characteristics in *appendix* 5.

8.3 Serious adverse reactions and events

SARs to pantoprazole:
Registered SARs are defined in *appendix* 4 and ARs not registered are discussed in *appendix* 6.

SARs to 10 ml of isotonic saline:

No SARs are associated with such small amount of intravenous isotonic saline.

8.3.1 Recording of serious adverse reactions and events

SARs will be recorded daily in the eCRF from the time of the first administration of trial medication and until 24 hours after last administration of trial medication or the patient is discharged from the ICU. If the patient is readmitted to the ICU and trial medication is re-introduced, SARs will be recorded. When a SAR is registered in the eCRF the coordinating investigator will be informed directly which will secure fast reporting of SAR. SARs in the two groups will be compared in the interim analyses and as an outcome measure. If a patient experiences a SAR he or she will be withdrawn from the trial. Daily registration will be continued and the follow-up will be conducted.

If a patient experiences SUSAR, the local investigator must report this without undue delay to the Sponsor (or delegated party). The patient will be withdrawn from the trial and the trial medication will be demasked. If a SUSAR is still reasonable after demasking, a report will be conducted describing onset and end of event, severity, the relation to the intervention, the actions taken and the outcome.

SAEs will not be recorded as an entity, because the majority of ICU patients will experience several SAEs during their critical illness. The most important SAEs will be captured in the secondary outcome measures (days alive without life-support). Patient charts, notes and lab reports will contain daily registrations of clinical data, which can be obtained on request from the medical authorities.

8.4 Reporting

Trial investigators are to report SUSARs without any delay to the sponsor, which in turn will report these to the Danish Health and Medicine Authorities 7 days at the latest after the report has been received.

9. Procedures, assessments and data collection

9.1 Inclusion procedure

9.1.1 Screening

All patients admitted to participating ICUs will be eligible for screening. In fertile women a negative urine-hCG or plasma-hCG must be present before enrolment.

9.1.2 Procedures for informed consent

Patients will be enrolled after consent is obtained according to national regulations. This procedure will be described by each participating country. The procedure for Danish patients is described in *appendix* 7.

9.2 Data collection

9.2.1 Method

Data will be obtained in eCRFs from a combination of patient files and national registers. For patients transferred from a trial ICU to a non-trial ICU, data related to the outcomes of interest will be collected after transferral e.g. by national registers, phone calls, and patient charts.

9.2.2 Timing

Appendix 8 shows an overview of the timing and all variables are defined in *appendix* 4.

Baseline variables (not collected in the screening procedure)

- Sex
- Age at randomisation/date of birth
- Date of admission to hospital and date and time to ICU
- Elective or emergency surgery during current hospitalization (y/n)
- Treatment of suspected or confirmed CDI during current hospital admission (y/n)
- Treatment with NSAID or acetylsalicylic acid at hospital admission (y/n)
- Treatment with anticoagulants at hospital admission (y/n)
- Intravenous thrombolysis within the previous 3 days (y/n)
- Co-morbidities (see definitions in *appendix* 4):
    - history of chronic lung disease
    - history of myocardial ischemia
    - history of severe chronic heart failure (NYHA 3-4)

    - history of chronic renal failure in the last year prior to hospital admission
    - treatment with at least 0.3 mg/kg/day of prednisolone equivalent for at least one month in the 6 month prior to ICU admission
    - active hematologic cancer
    - metastatic carcinoma
    - AIDS
- Values for simplified acute physiology score (SAPS) II 24 hours prior to randomisation (not covered above): heart rate, systolic blood pressure, core temperature, PaO2/ FiO2 ratio, urinary output, urea, white blood cell count, potassium, sodium, bicarbonate, bilirubin, Glasgow Coma Scale (GCS) score (*appendix* 9)
- Variables for severity organ failure assessment (SOFA) scoring 24 hours prior to randomisation not covered in SAPS II scoring: blood platelets, MAP, dose of noradrenalin, adrenalin and dopamine, use of inotropes, plasma creatinine (*appendix* 10)

Daily during ICU admission:

- Delivery of trial medication (y/n)
- Open label treatment with PPI/H2RA (y/n)
- Invasive or non-invasive mechanical ventilation (y/n)
- Circulatory support (infusion of vasopressor/inotropes) (y/n)
- Any form of renal replacement therapy (y/n)
- Onset of pneumonia (as defined in *appendix* 4) on this day (y/n)
- Treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, or enteral fidaxomicin) for suspected or proven CDI on this day (y/n)
- Acute myocardial ischemia (as defined in *appendix* 4) on this day (y/n)
- Enteral feeding on this day (y/n)
- Number of units of RBCs
- Overt bleeding episodes (hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate) (y/n)
- SARs (y/n) (*appendix* 4)

Bleeding form (only for patients with overt bleeding)

- Data on clinically important bleeding (overt GI bleeding as defined above and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) in the ICU:
    - a spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
    - start of vasopressor or a 20% increase in vasopressor dose
    - decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
    - transfusion of 2 units of packed red blood cells or more
- Origin of GI bleeding confirmed (y/n)
- Verification of ulcer/gastritis/esophageal varices (y/n)
- Haemostasis achieved/attempted by endoscopy/open surgery/coiling (y/n)

Follow-up 90 days after randomisation

- Death (y/n, if yes, date of death)

Follow-up 1 year after randomisation

- Death (y/n, if yes, date of death)

10. Data handling and record keeping

10.1 Data management

Data will be entered into an electronically, web-based eCRF from medical files and national registers by trial personnel.

10.2 Confidentiality

Each patient will receive a unique trial identification number. Trial investigators will receive personal username and passwords to access the randomisation system and the eCRF. Each site will only have access to site specific data.

Data will be handled according to the National Data Protection Agency, and is protected by the Danish national laws ‘Loven om behandling af personoplysninger’ and ‘Sundhedsloven’.

10.3 Biobanking

No biobank will be formed.

10.4 Access to data

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived at trial sites for 15 years. The clean electronic trial database file will be delivered to the Danish Data Archive and maintained for 15 years and anonymised if requested by the authorities.

11. Statistical analysis

90-day mortality and 1-year mortality have been chosen as outcomes for all-cause mortality. Besides landmark mortality, mortality 90 days and 1 year after last randomised patient have been considered, but due to practical and organisational matters, and lack of centralised registration, it will be difficult and for some countries impossible to get mortality data up to 3 years after enrolment of a patient.

11.1 Sample size estimation and power calculations

11.1.1 Sample size estimation for the primary outcome

Primary outcome measure

Assuming a baseline 90-day mortality of 25% [9] (see *appendix* 11) α=0.05 (two-sided), and β=0.1, 3350 patients (2 x 1675) will be needed to show a 20% relative risk reduction (RRR) or increase (RRI) corresponding to a 5% absolute risk reduction or risk increase in the primary outcome measure.

Trial Sequential Analysis [63, 64] of existing trials (n=16) has showed that 35% (1584 patients) of the required information size to detect or reject a 20% RRR corresponding to 4,575 patients has been accrued [31]. Consequently, there is an information gap of around 3000 patients assuming a 20% RRR in mortality (*appendix* 12). With the inclusion of an additional 3350 patients it is expected that the pooled effect will cross the boundary for benefit/harm or the boundary for futility.

11.1.2 Power estimations for secondary outcomes

Power estimations are based on 3350 included patients, a risk of type 1 error of 5%, and a minimal clinically relevant difference as stated:

Clinically important GI bleeding: 46% power (baseline 3% -> 2% = 33% RRR) for showing or discarding a numbers-needed-to-treat (NNT) of 100.
Pneumonia: 85% power (baseline 20% -> 16% = 20% RRR) for showing or discarding a NNT of 25.
CDI: 53% power (baseline 10% -> 8% = 20% RRR) for showing or discarding a NNT of 50.
Myocardial ischemia: 29% power (baseline 5% -> 4% = 20% RRR) for showing or discarding a NNT of 100

11.2 Statistical methods

The primary analysis will be conducted including the intention-to-treat population [65–67]. A sensitivity analysis will be conducted including the per-protocol population, excluding patients with a major protocol violation (patients who did not receive the allocated trial intervention at all, patients who did not receive the trial intervention for at least two days in a row, treatment with PPI or H2RA without clinically indication and withdrawal from trial intervention). Patients transferred to another ICU will be considered discharged from the ICU.
The primary analysis of all dichotomous outcomes will compare the outcome at 90 days after randomisation in the two groups by binary logistic regression analysis with adjustment for stratification variables [68]: site and active haematological cancer
A secondary analysis will be performed adjusting for stratification variables together with other known major prognostic co-variates: age, baseline SOFA score, and type of admission (medical, elective surgery or emergency surgery).
Further details will be provided in a statistical analysis plan.

11.2.1 Pre-planned subgroup analyses

We will compare the primary outcome measure in pre-specified subgroups defined according to 1) shock at randomisation (y/n), 2) mechanical ventilation at randomisation (y/n), 3) coagulopathy at randomisation or history of coagulopathy (y/n), 4) history of liver disease (y/n) 5) type of ICU admission (medical/surgery) and 6) SAPS II > 53 points (y/n).

11.2.2 Significance

A two-sided P value of less than 0.05 will be considered statistically significant.

11.2.3 Interim analysis

Interim analyses will be conducted after patient no. 1650 and 2500 has been followed for 90 days.

The DMSC will constitute its own plan of monitoring and meetings. The charter for the independent Data Monitoring and Safety Committee (DMSC) (*appendix* 3) defines the minimum of obligations and primary responsibilities of the DMSC as perceived by the SC, its relationship with other trial components, its membership, and the purpose and timing of its meetings.

The DMSC may recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function [69]. If an analysis of the interim data from 1650/2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the SC may stop the trial [67]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 15% RRR will not be an option as intervention effects less than 15% RRR of all-cause mortality may be clinically relevant as well.

11.2.4 Early stopping criteria

See previous section

11.2.5 Accountability procedure for missing data/population for analysis

If less than 5% of data are missing on any primary or secondary outcome, a complete case analysis without input of missing values will be performed. If missing data are more than 5%, a blinded statistician will assess whether data are 'missing completely at random' (MCAR criterion) based on a rational assessment of the pattern of missing data [70]. Little's test will be used if there remains doubt [71]. If it is concluded that data are not 'missing completely at random', multiple imputation using chained equations will be performed by creating ten input data sets under the assumption that the data are missing data at random (MAR criterion) [72, 73]. We will use outcomes and the most important baseline characteristics in the multiple imputation. The exact variables to be used to estimate the missing values will be outlined in

the detailed statistical analysis plan: If multiple imputation is used, then the primary result of the trial will be based on these data. The unadjusted, non-imputed analysis will also be made available. If multiple imputation is used, we use a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the 'best-worst-case' scenario it is assumed that all patients lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived, had no serious adverse reactions etc.); and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived; have had a serious adverse reaction etc.). Conversely, in the 'worst-best-case' scenario, it is assumed that all patients who were lost to follow up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two standard deviations (SD) of the group mean, and a 'harmful outcome' will be defined as the group mean minus two SD of the group mean.

12. Quality control and quality assurance

The coordinating investigator will be responsible for organizing the trial sites including education of local investigators, research nurses, and other trial site personnel before the initiation of the trial. This education will be continuously documented and two annual investigator meetings will be planned.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of patients and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial patients.

12.1 Monitoring of the intervention groups

The trial will be externally monitored following a monitoring plan developed in collaboration with the GCP Unit in Copenhagen, which will coordinate the monitoring done by local GCP units and/or monitors in all countries. A centralised day-to-day monitoring of the eCRF will be done by the coordinating investigator or her delegates.

13. Legal and organisational aspects

13.1 Finance

13.1.1 Trial funding

The SUP-ICU trial is funded by the Innovation Fund Denmark (4108-00011A). The funding sources will have no influence on trial design, trial conduct, data handling, data analysis or publication.

13.1.2 Compensation

Trial sites will be given DKR 1500 (200 EUR) in case money for each patient with 90-day follow-up to compensate for the increased workload participation infers.

13.2 Insurance

In Denmark, all trial participants are insured by the Patient Insurance Association. Patient insurance will be ensured before initiating the trial in each participating countries. Costs for insurance will be sought financed by funding.

13.3 Plan for publication, authorship and dissemination

13.3.1 Publication and authorship

The trial will be registered on www.clinicaltrials.gov. The final protocol will be published as a design and rationale paper including the plan for analyses. Upon trial completion the main manuscript with trial results whether positive, negative or neutral will be submitted for a peer-reviewed publication, to one of the major clinical journals. Furthermore the results will be published at the SUP-ICU home page (www.sup-icu.com).

The listing of authors will be as follows: M Krag will be the first author, A Perner the second, J Wetterslev the third, M Wise will be the fourth author and the next authors will be the national investigators according to the number of included patients per country, then the trial statistician and trial site investigators dependent on the number of included patients per site. MH Møller will be the last and corresponding author, and 'the SUP-ICU trial co-authors' will be written.

The SC will grant authorship depending on personal input according to the Vancouver definitions. If a trial site investigator is to gain authorship, the site has to include 50 patients or

more. If the site includes 100 patients or more, two authorships will be granted per trial site, 150 patients will give 3 authorships per trial site and so on.
The DMSC and investigators not qualifying for authorship will be acknowledged with their names under the “SUP-ICU Trial investigators’ in an *appendix* to the final manuscript.
Funding sources will have no influence on data handling or analyses or writing of the manuscript.

13.4 Spin-off projects

Spin-off projects will be encouraged and conducted when approved by the SC. Presently no spin-off projects have been developed.

13.5 Intellectual property rights

Sponsor and primary investigator is MH Møller. Therefore no contract on intellectual property rights is indicated. The initiative for the SUP-ICU trial has been taken by MH Møller and A Perner and by doctors at multiple ICUs, none of whom have affiliations to institutions that may have economic interests in the trial results. Contracts between national investigators and Sponsor and between site investigators and Sponsor will be signed before conduct of the trial.

13.6 Organisational framework

The trial is part of the SUP-ICU research programme (www.sup-icu.com) and Centre for Research in Intensive Care (CRIC).

13.7 Trial timeline

2014 – November 2015: Governance approval applications, education of trial sites, other preparations
December 2015: First Danish patient enrolled
February 2015: Commencement of inclusion in other countries
November 2017: Last patient enrolled
January 2018: Follow-up completed
May 2018: Data analysis and submission for publication

14. Appendix

Appendix 1: Research Programme Organisation

Appendix 2: Undesirable effects of pantoprazole

Appendix 3: Charter for the independent Data Monitoring and Safety Committee

Appendix 4: Definitions

Appendix 5: Summary of product characteristics

Appendix 6: Adverse reactions not registered

Appendix 7: Informed consent in Denmark

Appendix 8: Timeline

Appendix 9: SAPS II Score

Appendix 10: SOFA score

Appendix 11: Power estimations

Appendix 12: Trial sequential analysis

Appendix 13: International Committee of Medical Journal Editors (ICMJE) form for potential conflicts of interest

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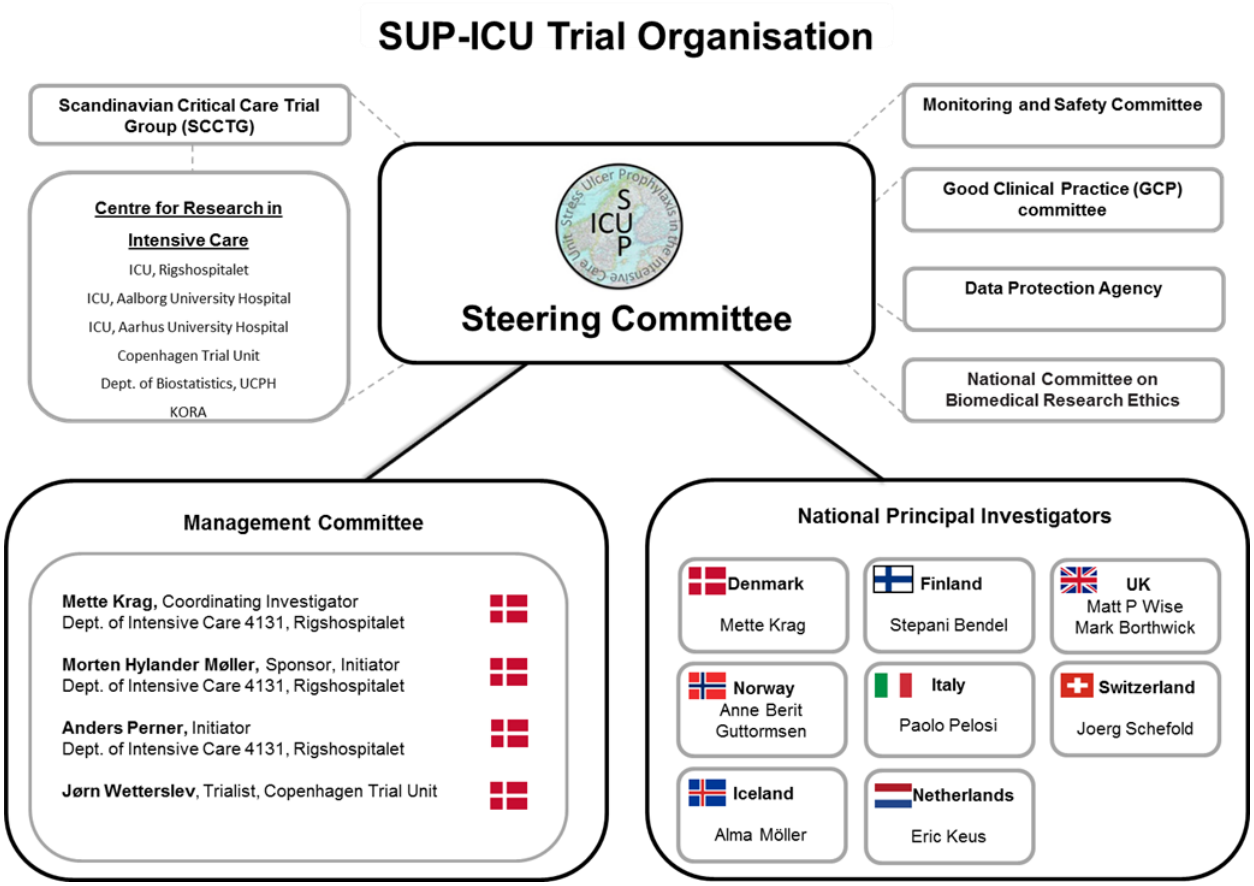
Appendix 1. Trial organisation



Appendix 2. Undesirable effects of pantoprazole

Approximately 5% of patients can be expected to experience adverse drug reactions. The most commonly reported adverse drug reactions are diarrhoea and headache, both occurring in approximately 1% of patients.
For all adverse reactions reported from post-marketing experience, it is not possible to apply any adverse reaction frequency and therefore they are mentioned with a “not known” frequency.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency **System Organ Class**	**Common***	**Uncommon***	**Rare***	**Very rare***	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombo-cytopenia; Leukopenia Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemi as and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia (see section 4.4) Hypocalcaemia in association with hypomagnesemia; Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorien-tation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)

Nervous system disorders		Headache Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders		Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
Hepatobiliary disorders		Liver enzymes increased (transaminas-es, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Ery-thema multiforme; Photosensitivity
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

*Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Appendix 3. Charter for the independent Data Monitoring and Safety Committee (DMSC)

ClinicalTrials.gov Identifier: NCT02467621
Research ethical committee no: H-15003141

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the steering committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the SUP-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of patients, their management, improving adherence to protocol-specified regimens and retention of patients, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC is planned by protocol to meet physically in order to evaluate the planned interim analyses of the SUP-ICU trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC (to be announced). The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail in order to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of Serious Adverse Reactions (SARs) yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions if suggested by the data, see section on ‘closed sessions’. The recommendations of the DMSC regarding stopping,

continuing or changing the design of the trial should be communicated without delay to the SC of the SUP-ICU trial. As fast as possible, and no later than 48 hours, the SC has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the SC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomised clinical trials.

DMSC Members

Anders Åneman, MD PhD
Tim Walsh, professor, MD, PhD

DMSC Biostatistician

Aksel Karl Georg Jensen, Section of Biostatistics, University of Copenhagen

Conflicts of interest

DMSC members will fill in and sign a declaration of conflicts of interests see *appendix* 13. DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the SUP-ICU trial.
The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the contract research organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.
The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.
The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the SC will appoint the replacement(s).

Formal interim analyses meeting

Two formal interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-day follow-up data of 1650 (approximately 50% of sample size estimation) and 2500 (approximately 75% of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the SC.

Closed reports will include analysis of the primary outcome measure. In addition, analyses of the secondary outcome measures and SARs will also be reported. These closed reports will be prepared by independent biostatistician being a member of the DMSC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the SC to continue, hold or terminate the trial.

Interim analyses will be conducted after patient no. 1650 and 2500 has been followed for 90 days. The DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function [69]. If an analysis of the interim data from 1650/2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial [67]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 15% RRR will not be

an option as intervention effects less than 15% RRR of all-cause mortality may be clinically relevant as well.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The SC is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the protocol. For the two intervention groups, the DMSC will evaluate data on:

<u>The primary outcome measure</u>

Mortality 90 days after randomisation of each patient ("landmark mortality").

<u>The secondary outcome measures</u>

- Proportion of patients with one or more of the following adverse events: clinically important gastrointestinal (GI) bleeding, pneumoni, *clostridium difficile* infection (CDI), and acute myocardial ischemia
- Proportion of patients with clinically important GI bleeding
- 1 year mortality post-randomisation
- The occurrence of SARs in the ICU

The DMSC will be provided with these data from the coordinating centre as:

Number of patients randomised

Number of patients randomised per intervention group

Number of patients stratified pr. stratification variable per intervention group

Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about SARs occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC
The DMSC will be provided with a file containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

Row 2 to N (where N-1 is the number of patients having entered the trial) each contains the data of one patient.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

1. screening_id: a number that uniquely identifies the patient

2. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received

3. clin_imp_bleed: clinically important GI bleeding (1 if the patient had one or more episodes and 0 if the patient did not)

4. pneumonia: onset of pneumonia in the ICU after randomisation (1 = one or more episodes, 0= no episodes)

5. clostridium: *clostridium difficile* infection (1 = one or more episodes, 0= no episodes)

6. ami: acute myocardial ischemia in the ICU (1 = one or more episodes, 0= no episodes)

7. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SARs)

Appendix 4. Definitions

Definition of stratification variables

Site: all participating intensive care units (ICUs) will be assigned a number identifying the department.

Haematological malignancy includes any of the following:

- leukemia: Acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL).
- lymphoma: Hodgkin's disease, Non-Hodgkin lymphoma (e.g. small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), hairy cell leukemia (HCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), post-transplant lymphoproliferative disorder (PTLD), T-cell prolymphocytic leukemia (T-PLL), B-cell prolymphocytic leukemia (B-PLL), Waldenström's macroglobulinemia, other NK- or T-cell lymphomas
- Multiple myeloma/plasma cell myeloma

Definition of inclusion criteria

Acute admission to the ICU: a non-planned admission. It does not include planned recovery after surgery or similar planned admissions. ICU admission does not include admissions to semi intensive care, intermediate intensive care or similar beds.

Age: the age of the patient in whole years at the time of randomisation. The age will be calculated from date of birth

Shock: at least one of the following:

- systolic pressure < 90 mmHg
- mean arterial pressure < 70 mmHg
- use of vasopressors or inotropes (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosimendan)
- lactate > 4 mmol/l

Renal replacement therapy: acute or chronic intermittent or continuous renal replacement therapy

Patients with expected duration of invasive mechanically ventilation > 24 hours: the treating clinician estimates that the patient will be invasively mechanically ventilated for more than 24 hours. When in doubt of this forecast the patient should be enrolled

Coagulopathy: platelets < 50 x 10^9/l or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds documented within the last 24 hours

Treatment with anticoagulant drugs: ongoing treatment with: Dipyridamole, vitamin K antagonists, ADP-receptor inhibitors, therapeutic doses of low molecular weight heparin, new oral anticoagulant drugs, intravenous direct thrombin (II) inhibitors and similar drugs. Acetylsalicylic acid (all doses) and low molecular weight heparin in prophylactic doses are NOT included

History of coagulopathy: coagulopathy defined as platelets < 50 x 10^9/l AND/OR INR > 1.5 AND/OR PT > 20 seconds within 6 months prior to hospital admission.

History of chronic liver disease: portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history

Definition of exclusion criteria

Contraindications to proton pump inhibitors (PPI): any history of intolerance to PPI or additives or treatment with atazanavir (HIV medication)

Ongoing treatment with PPI and/or histamine-2-receptor antagonists (H2RA): ongoing is defined as treatment not being discontinued at ICU admission. If clinicians do not find indication for continuation of treatment with PPI/H2RA during ICU stay, the patient will be eligible for inclusion.

GI bleeding during current hospital admission: GI bleeding of any origin (both upper and lower) documented in the patient charts

Peptic ulcer: peptic ulcer confirmed by endoscopy or other method during current hospital admission

Organ transplant: any kind of organ transplant during current hospital admission.

Withdrawal from active therapy or brain death: patients where withdrawal or brain death is documented in the patient charts

Known pregnancy: fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma-hCG

Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain necessary consent before inclusion of the patient according to the national regulations

Definition of baseline variables

Sex: the genotypic sex of the patient

Age: defined in inclusion criteria

Date of admission to hospital: the date of admission to the first hospital the patient was admitted to during the current hospital admission

Elective surgery: surgery during current hospital admission scheduled 24 hours or latter in advance

Emergency surgery: surgery during current hospital admission that was added to the operating room schedule 24 hours or less prior to surgery

Medical admission: when no surgery has been performed during current hospital admission OR surgery has been performed more than 1 week prior to ICU admission

Treatment with anticoagulants at hospital admission and at ICU admission: anticoagulants are defined in inclusion criteria

Treatment with non-steroidal anti-inflammatory drugs (NSAID) and acetylsalicylic acid at hospital admission: treatment with all doses of these drugs at hospital admission

Treatment with intravenous thrombolysis: treatment with all kinds of intravenous thrombolysis within 3 days prior to randomisation

Coagulopathy: defined in inclusion criteria

Treatment of suspected or confirmed *Clostridium difficile* infection (CDI) during current hospital admission

Coexisting illness must have been present in the past medical history prior to ICU admission and are defined as follows:

- Chronic lung disease: chronic obstructive pulmonary disease (COPD), asthma or other chronic lung disease or treatment with any relevant drug indicating this at admission to hospital
- Previous myocardial infarction: history of myocardial infarction
- Chronic heart failure: New York Heart Association Functional Class (NYHA) III-IV. NYHA III: The patient has marked limitations in physical activity due to symptoms (fatigue, palpitation or dyspnoea) even during less than ordinary activity (walking short distances 20-100 m. or walking up stairs to 1st floor). The patient is only comfortable at rest. NYHA class 4: The patient is not able to carry out any physical activity (without discomfort (fatigue, palpitation or dyspnoea). Symptoms are present even at rest and the patient is mostly bedbound
- History of chronic renal failure: need of any form of chronic renal replacement therapy within the last year
- Liver disease: defined in baseline variables
- History of coagulopathy: defined in baseline variables
- Immunosuppression: patients treated with at least 0,3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission
- Metastatic cancer: proven metastasis by surgery, CT scan or any other method
- Hematologic malignancy: defined as stratification variable
- AIDS: HIV positive patients with one or more HIV defining diseases such as pneumocystis jerovechii pneumonia, Kaposi's sarcoma, Lymphoma, tuberculosis or toxoplasma infection

The Simplified Acute Physiology Score (SAPS II) [74] (*appendix* 9) is based on the most extreme (highest or lowest) values from 24 hours prior to randomisation. The score consists of 17 variables: 12 physiologic variables, age, type of admission and 3 variables related to underlying disease to give a total score ranging from 0 to 163, with higher scores indicating greater severity of illness. The score will be calculated from data from the 24 hours prior to randomisation

The Sequential Organ Failure Assessment (SOFA) Score [75] (*appendix* 10) will be calculated from raw physiology and treatment data from the 24 hours prior to randomisation. The SOFA Score consists of weightings for six organ systems to give a total score ranging from 0 to 24, with higher scores indicating a greater degree of organ failure.

Definition of daily collected variables:
Delivery of trial medication: confirmation of administration of the trial drug

Treatment with PPI or H2RA: prescription of any of these drugs in any dose (major protocol violation if the treatment is initiated (e.g. as prophylaxis) without clinical indication (e.g. gastrointestinal bleeding)

Mechanical ventilation: invasive and non-invasive mechanical ventilation including continuous mask CPAP or CPAP via a tracheotomy. Intermittent CPAP is NOT mechanical ventilation.

Circulatory support: continuous infusion of vasopressor or inotrope (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosimendan)

Renal replacement therapy: any form of renal replacement therapy on this day. In patients receiving intermittent renal replacement therapy days between treatments are included

Clinically important GI bleeding, onset of pneumonia, CDI, and acute myocardial ischemia in the ICU are defined as outcomes

Treatment with enteral feeding: any dose of enteral feeding (including oral nutritional intake) during the day

Units of red blood cells: cumulated number of units of red blood cells transfused during the day

Serious adverse reactions (SARs) are defined below

Definition of bleeding variables:
Confirmed diagnosis: diagnosis/origin of bleeding confirmed by endoscopy or other method

Verification of ulcer/gastritis/bleeding oesophageal varices: confirmation of one of the three specific diagnoses by endoscopy or other method

Haemostasis achieved or attempted: documentation in patient charts of haemostasis achieved or attempted by endoscopy, open surgery or coiling

Definitions of outcome measures

Primary outcome:

90-day mortality: death from any cause within 90 days following the day of randomisation

Secondary outcomes:

Proportion of patients with one or more of the following adverse events: clinically important GI bleeding, pneumonia, CDI, and acute myocardial ischemia. The events are defined as follows:

Clinically important GI bleeding: overt GI bleeding* and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) in the ICU

a) spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
b) start of vasopressor or a 20% increase in vasopressor dose
c) decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
d) transfusion of 2 units of packed red blood cells or more

*Overt GI bleeding: hematemesis, coffee ground emesis, melena, haematochezia or bloody nasogastric aspirate

Pneumonia: episodes of newly confirmed pneumonia according to the modified CDC criteria [76]

- Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):
  1. new or progressive and persistent infiltrate
  2. consolidation
  3. cavitation

- AND at least one of the following:
  1. fever (>38°C) with no other recognised cause
  2. leukopenia (white cell count < 4 x 109/l) or leucocytosis (white cell count >12 x 109/l)
- AND at least two of the following

1. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements
2. new onset or worsening cough, or dyspnoea, or tachypnoea
3. rales or bronchial breath sounds
4. worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand)

CDI: Treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, enteral fidaxomicin) for suspected or proven CDI

Acute myocardial ischemia: ST-elevation myocardial infarction, non-ST elevation myocardial infarction or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) AND receiving treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) or initiation/increased antithrombotic treatment)

Proportions of patients with clinically important GI bleeding: proportion of patients with one or more episodes of clinically important GI bleeding as defined above

Proportion of patients with one or more infectious adverse events: proportion of patients with one or more episodes of pneumonia or CDI

1-year mortality: landmark mortality 1 year post-randomisation

Duration of life support in the ICU: the number of days alive and free from respiratory or circulatory support and of renal replacement therapy as defined below. The outcome will be days alive without use of mechanical ventilation, circulatory support or renal replacement therapy in the 90-day period, and will be defined as the percentage of days without mechanical ventilation, circulatory support and renal replacement therapy (as defined in daily collected variables) in the 90 days after randomisation

Serious adverse reactions: number of serious adverse reactions as defined below

The elements of all composite outcomes will be reported in the supplementary material

A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-benefit vs cost-minimisation analyses).

Definitions of serious adverse reactions

A serious adverse reaction (SAR) is defined as any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity.

Patients will be monitored for onset of SARs occurring between the first dose of trial medication and until discharge from the ICU. If a patient is withdrawn from the trial intervention, SARs will be recorded for 24 hours after the last dose of trial medication or discharge from ICU. If the patient is readmitted to the ICU and trial intervention is reintroduced, data collection for SARs will be resumed. If a patient experiences a SAR the patient will be withdrawn from the trial intervention but data collection and follow-up will be continued (see section 4.3.2)

SARs will be defined as follows:

Anaphylactic reactions defined as urticaria and at least one of the following

- Worsened circulation (>20% decrease in blood pressure or >20% increase in vasopressor dose)
- Increased airway resistance (>20% increase in the peak pressure on the ventilation)
- Clinical stridor or bronchospasm
- Subsequent treatment with bronchodilators

Agranulocytosis is defined as any new, acute and severe drop in granulocytes to $< 0.5 \times 10^9/l$ requiring active monitoring or treatment

Pancytopenia is defined as any new, severe drop in red blood cells, white blood cells and platelets requiring active monitoring or treatment

Acute hepatic failure is defined as severe and progressing hepatic failure as judged by the treating doctor or the investigator

Steven-Johnson syndrome and toxic epidermal necrolysis are defined as severe dermatological reactions with a skin biopsy confirming the diagnosis

Interstitial nephritis is defined as a nephritis affecting the interstitium of the kidneys surrounding the tubules with a kidney biopsy confirming the diagnosis

Angioedema (Quincke's oedema) is defined as a vascular reaction involving the deep dermis, subcutaneous or submucosal tissues, resulting in a characteristic localized oedema.

Adverse reactions not registered will be discussed in *appendix* 6.

Appendix 5. Translation of the Danish summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

for

Pantoprazol “Actavis”, powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazol “Actavis” 40 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate)

Excipients with known effect:
Each vial contains 5.0 mg of sodium citrate dihydrate and sodium hydroxide q.s.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially “sodium free”.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White or almost white, uniform porous cake.

For the solution reconstituted with 10 ml of 0.9% NaCl solution the pH is approximately 10 and the osmolality is approximately 382 mOsm/Kg

For the solution reconstituted with a further 100 ml of 0.9% NaCl solution or 5% glucose solution the pH is approximately 9 and 8.5, respectively

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Reflux oesophagitis
- Gastric and duodenal ulcer
- Zollinger – Ellison Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

This medicine should be administered by a healthcare professional and under appropriate medical supervision.

The intravenous administration of pantoprazole is recommended only if oral application is not appropriate. Data are available on intravenous use for up to 7 days. Therefore as soon as oral therapy is possible, treatment with pantoprazole i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Posology

Gastric and duodenal ulcer, reflux oesophagitis
The recommended intravenous dose is one vial of pantoprazole (40 mg) per day.

Zollinger-Ellison Syndrome and other pathological hypersecretory conditions
For the long-term management of Zollinger-Ellison Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg of pantoprazole i.v. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

In case a rapid acid control is required, a starting dose of 2 x 80 mg of pantoprazole i.v. is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.

Special populations
Paediatric population
The experience in children is limited. Therefore, pantoprazole i.v. is not recommended for use in patients below 18 years of age until further data become available.

Hepatic impairment:
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section 4.4).

Renal impairment:
No dose adjustment is necessary in patients with impaired renal function.

Elderly
No dose adjustment is necessary in elderly patients.

Method of administration
A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. For instructions for preparation see section 6.6. The prepared solution may be administered directly or may be administered after mixing it with 100 ml of 9 mg/ml (0.9%) sodium chloride injection, or 50 mg/ml glucose (5%) solution for injection.

After preparation the solution must be used within 12 hours (see section 6.3).

The medicinal product should be administered intravenously over 2 – 15 minutes.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In presence of alarm symptoms
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Hepatic impairment

In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise in the liver enzymes, the treatment should be discontinued (see section 4.2).

Co-administration with atazanavir
Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria (e.g. *Salmonella* and *Campylobacter* and *C.difficile*).

Sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pantoprazole on the absorption of other medicinal products
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependant bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

HIV medications (atazanavir)
Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon or warfarin)
Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

Other interactions studies
Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with drugs also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Breast-feeding
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

4.7 Effects on ability to drive and use machines

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1% of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (<1/10,000 to <1/1,000), very rare (1/10,000) not known (cannot be estimated from the available data). For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency / **System organ class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombo-Cytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemia and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia; Hypocalcaemia in association with hypomagnesaemia; Hypokalaemia

Frequency / System organ class	Common	Uncommon	Rare	Very rare	Not known
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination: Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision/blurred vision		
Gastrointestinal disorders		Diarrhoea; Nausea/ vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort.			
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash/ exanthema/ eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photo-sensitivity
Musculo-skeletal and connective tissue disorders			Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable.

In case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02.

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H^+/K^+-ATPase enzyme i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies.

5.2 Pharmacokinetic properties

General Pharmacokinetics
Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Distribution
Pantoprazole's plasma protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

Elimination

The substance is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were few cases of subjects with delayed elimination. Because of specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest are excreted in the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

Characteristics in patients/special groups of subjects:
Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (2-3 hours), excretion is still rapid and thus accumulation does not occur.
Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Paediatric population
Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

5.3 Preclinical safety data

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the two-year rodent studies an increased number of liver tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at does above 5 mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium citrate dihydrate

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale: 3 years

After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25ºC. The reconstituted, or reconstituted and diluted medicinal product should not be refrigerated.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the vial in the outer carton to protect from light.
For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

15 ml, type I, colourless glass vial, sealed with a grey chlorobutyl stopper and an aluminium flip-off cap, containing 40 mg pantoprazole powder for solution for injection.

Pack sizes: 1, 5, 10 and 20 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A ready-to-use intravenous solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the lyophilised powder. The reconstituted solution should be clear and colourless. This solution may be administered directly or may be administered after mixing it with 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution

Pantoprazol “Actavis” 40 mg powder for solution for injection should not be prepared or mixed with solvents other than those stated.

This medicine should be administered intravenously over 2- 15 minutes.

The content of the vial is for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

Appendix 6. Adverse reactions not registered

Thrombocytopenia will not be registered as a serious adverse reaction (SAR) since it is a frequent condition among critically ill patients and is a part of the inclusion criteria (coagulopathy).

Increased plasma levels of bilirubin, (jaundice) and liver enzymes (hepatocellular injury) is not registered as they in themselves are not considered serious conditions. The potential serious consequence hepatic failure will be registered daily as a SAR.

Hyponatremia, hypokalaemia, hypomagnesaemia and hypocalcaemia will not be registered as electrolyte disturbances as they are frequent among ICU patients. These conditions are monitored and treated daily in all ICU patients. According to the summary of product characteristics, hypomagnesaemia will not be relevant until treatment for at least three months and in most cases one year.

Leukopenia will not be registered. Reduced white blood cell counts are frequent among ICU patients and can be associated with many different systemic or hematological disorders in critically ill patients.

Renal and urinary disorders will not be registered as they are not considered serious conditions in themselves, but the potential serious consequence will be reflected in the outcome measure days alive without use of renal replacement therapy.

The following possible adverse reactions will not be registered as SARs as they are not considered serious conditions:

Hyperlipidaemia, lipid increases, weight changes, taste disorders
Sleep disorders, depression, disorientation, hallucination, confusion, headache, dizziness
Paraesthesia, blurred vision
Nausea, vomiting, abdominal distension, constipation, dry mouth, abdominal pain and discomfort
Rash, exanthema, pruritus, erythema multiforme, photosensitivity, urticarial, hypersensitivity
Arthralgia, myalgia, asthenia, fatigue and malaise
Reproductive system, breast disorders, gynecomastia
Injection site thrombophlebitis
Body temperature increased

Oedema peripheral

Fracture of the hip, wrist or spine (treatment > 1 year)

Appendix 7. Informed consent, Denmark

In Denmark temporarily incompetent patients will be enrolled after informed consent from two physicians, who are independent of the trial (trial guardians). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and general practitioner or the Regional Medical Officer of Health according to Danish law. Patients, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

Lack of informed consent from the general practitioner
If the general practitioner does not want to make up his/her mind about the patient's participation in the trial, e.g. if he/she does not have the knowledge to make the decision or for any other reasons the patient will continue in the trial until informed consent can be obtained from the patient him-/herself. If the general practitioner cannot be reached the Regional Medical Officer of Health will be contacted for consent.

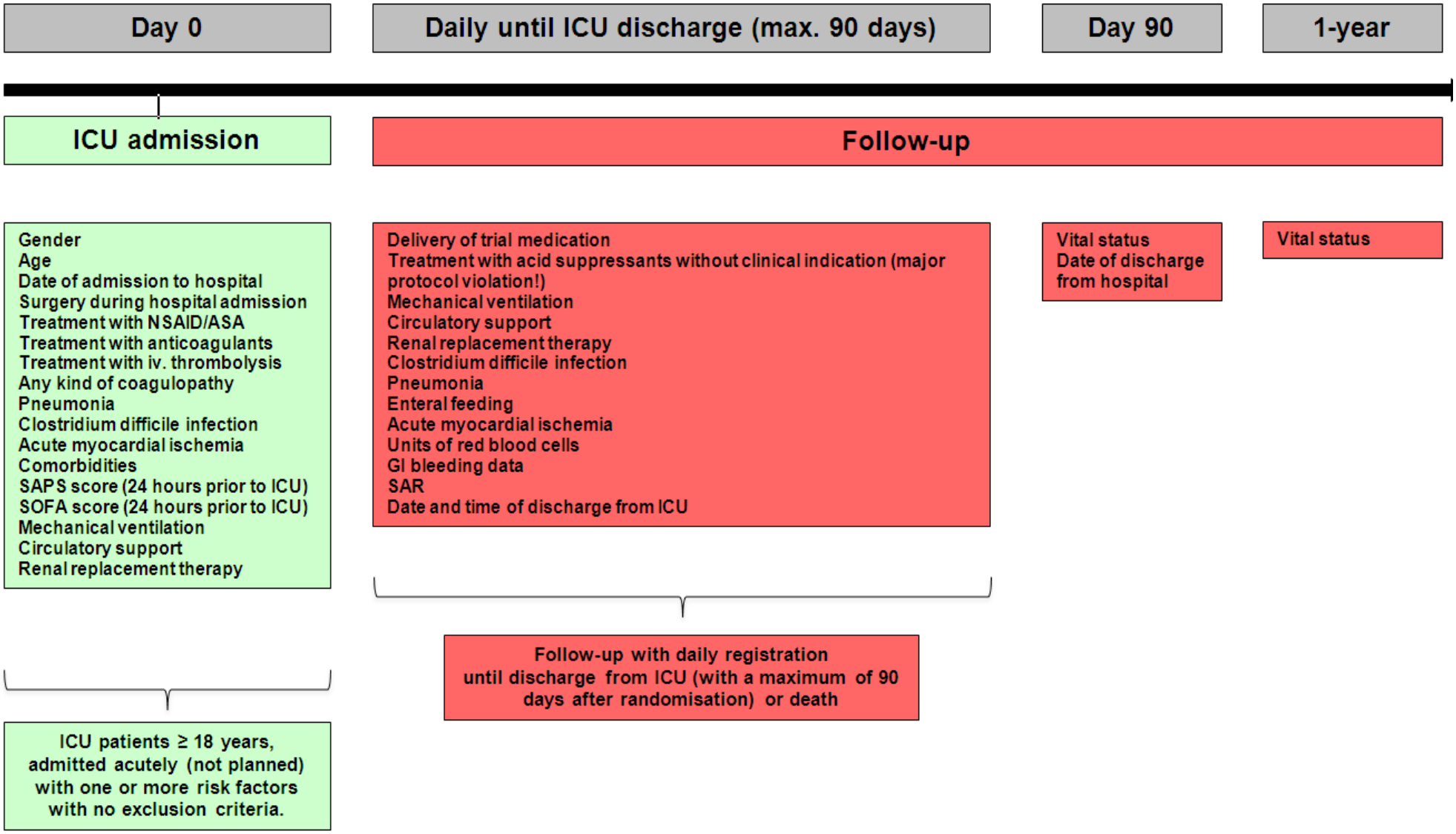
Lack of informed consent from the patient's next of kin
If it is not possible (i.e. contact cannot be obtained) - after obtaining informed consent from two independent physicians and from the patient's general practitioner/the Regional Medical Officer of Health - to obtain informed consent from the patient's next of kin, the patient will continue in the trial until informed consent can be obtained from the patient him-/herself.

Lack of informed consent from the patient's next of kin and the patient deceases
If it is not possible (i.e. contact cannot be obtained) - after obtaining informed consent from two independent physicians and from the patient's general practitioner/the Regional Medical Officer of Health - to obtain informed consent from the patient's next of kin, the patient will continue in the trial until informed consent can be obtained from the patient him-/herself. If the patient deceases before informed consent is obtained, or remains in a permanent state of incompetence, the collected data will be kept and trial outcomes will be collected centrally.

Deviation from the standard informed consent

According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

Appendix 8. Timeline



Appendix 9. SAPS II scoring sheet [74]

Part 1

Variable	Points:	26	13	12	11	9	7	6	5	4	3	2	0
Age													< 40
Heart rate					< 40							40-69	70-119
Systolic blood pressure mmHg			< 70						70-99				100-199
Body temperature													
°C													< 39
°F													<102.2
Only if ventilated													
PaO_2 mmHg/FiO_2					< 100	100-199		≥200					
PaO_2 kPa/FiO_2					<13.3	13.3-26.5		≥26.6					
Urinary output ml/day					<500					500-999			> 1000
Serum urea level													
mmol/l													< 10.0
(g/dl)													(< 0.6)
WBC				<1.0									1.0-19.9
10^9/l													
Serum potassium											<3.0		3.0-4.9
mmol/l													
Serum sodium mmol/l									<125				125-144
Serum bicarbonate mEq/l									<15		15-19		≥20
Bilirubin													
umol/l													< 68.4
(mg/dl)													(<4.0)
Glascow coma scale score	<6		6-8				9-10		11-13				14-15
Chronic disease													
Type of admission													Scheduled surgical

Part 2

Variable	1	2	3	4	6	7	8	9	10	12	15	16	17	18
Age						40-59				60-69	70-74	75-79		≥80
Heart rate				120-159		≥160								
Systolic blood pressure mmHg		≥200												
Body temperature °C °F			≥39.0 ≥102.2											
Only if ventilated PaO_2 mmHg/FiO_2 PaO_2 kPa/FiO_2														
Urinary output ml/day														
Serum urea level mmol/l (g/dl)					10.0-29.9 0.60-1.79				≥30.0 ≥1.80					
WBC 10^9/l			≥20.0											
Serum potassium mmol/l			≥5.0											
Serum sodium mmol/l	≥145													
Serum bicarbonate mEq/l														
Bilirubin umol/l (mg/dl)				68.4-102.5 (4.0-5.9)				≥102.6 (≥6.0)						
GCS score														
Chronic disease								Metastatic cancer	Hematologic malignancy				AIDS	
Type of admission					Medical		Unsceduled surgical							
Sum of points														

Appendix 10. SOFA score [75]

	0	1	2	3	4
Respiraiton					
PaO_2/FiO_2					
(mmHg)	≥ 400	< 400	< 300*	< 200†	< 100†
(KPa)	≥ 53	< 53	< 40*	< 27†	< 13†
Coagulation					
Platelets (x 10^3/mm3)	≥ 150	101-150	51-100	21-50	≤ 20
Liver					
Bilirubin					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
(umol/l)	< 20	20-32	33-101	102-204	> 204
Cardiovascular					
Hypotension*			Dopamine ≤ 5☼ **OR**	Dopamine ≥ 5☼ **OR**	Dopamine > 15☼ **OR**
(MAP)	≥ 70	< 70	Dobutamine (any dose) **OR**	Norepinephrine ≤ 0.1☼ **OR**	Norepinephrine > 0.1☼ **OR**
			Milrirone (any dose) **OR**	Adrenaline ≤ 0.1☼ **OR**	Adrenaline > 0.1☼
			Levosimendan (any dose) **OR**	Vasopression (any dose) **OR**	
				Phenylephrine (any dose) **OR**	
CNS					
Glascow coma scale score	15	13-14	10-12	6-9	< 6
Renal					
Creatinine					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(umol/l)	< 110	110-170	171-299	300-440	>440
OR					
Urine output				<500 ml/day	<200 ml/day

* without respiratory support
† with respiratory support
☼Adrenergic agents administered for at least one hour (doses given are in ug/kg/min).

Appendix 11. Power estimation

All power estimations have been calculated on data from the international SUP-ICU 7-day inception cohort study[57].
Since we do not know whether treatment with acid suppressants reduce or increase mortality, a number of scenarios have been considered (+/- 20 relative risk reduction):

1) 25.0% mortality 90 days after inclusion among patients with:
At least one risk factor*
No acid suppressants at ICU admission
Treatment with acid suppressants during ICU admission
No clinically important bleeding** during ICU admission

Power estimations:

ARR	Power	Patients per group
- 5%	80%	1091
	90%	1461
+ 5%	80%	1248
	90%	1671

We do not know whether PPI benefits or harms the patients, and need to include both scenarios. With 1671 patients in each group we will be able to show an absolute increase in risk of 5% with 90% power at the primary outcome, but also an absolute risk reduction of 5% with 90% power. The sample size has been calculated on patients fulfilling inclusion and exclusion criteria in the SUP-ICU trial and because few patients were not treated with acid suppressants during ICU admission, the estimation is based on the group receiving acid suppressants (intervention group)

2) 25.9% mortality 90 days after inclusion among patients with:
At least one risk factor*
No acid suppressants at ICU admission
Treatment with acid suppressants during ICU admission
Bleeding (overt or clinically important**) or no bleeding during ICU admission

Power estimations:

ARR	Power	Patients per group
- 5,2%	80%	1034
	90%	1384
+5,2%	80%	1180
	90%	1579

3) 29.2% mortality 90 days after inclusion among patients with:

At least one risk factor*

Acid suppressants and no acid suppressants at ICU admission

Treatment with acid suppressants during ICU admission

No bleeding (overt or clinically important**) during ICU admission

Power estimations:

ARR	Power	Patients per group
- 5,8%	80%	901
	90%	1206
+5,8%	80%	1014
	90%	1357

4) 30.5% mortality 90 days after inclusion among patients with:

At least one risk factor*

Acid suppressants or no acid suppressants at ICU admission

Treatment with acid suppressants during ICU admission

Bleeding (overt or clinically important**) or no bleeding during ICU admission

Power estimations:

ARR	Power	Patients per group
- 6,1%	80%	837
	90%	1120
+6,1%	80%	937
	90%	1254

*Risk factors are: shock, renal replacement therapy, coagulopathy and coagulopathy and liver disease as comorbidities)

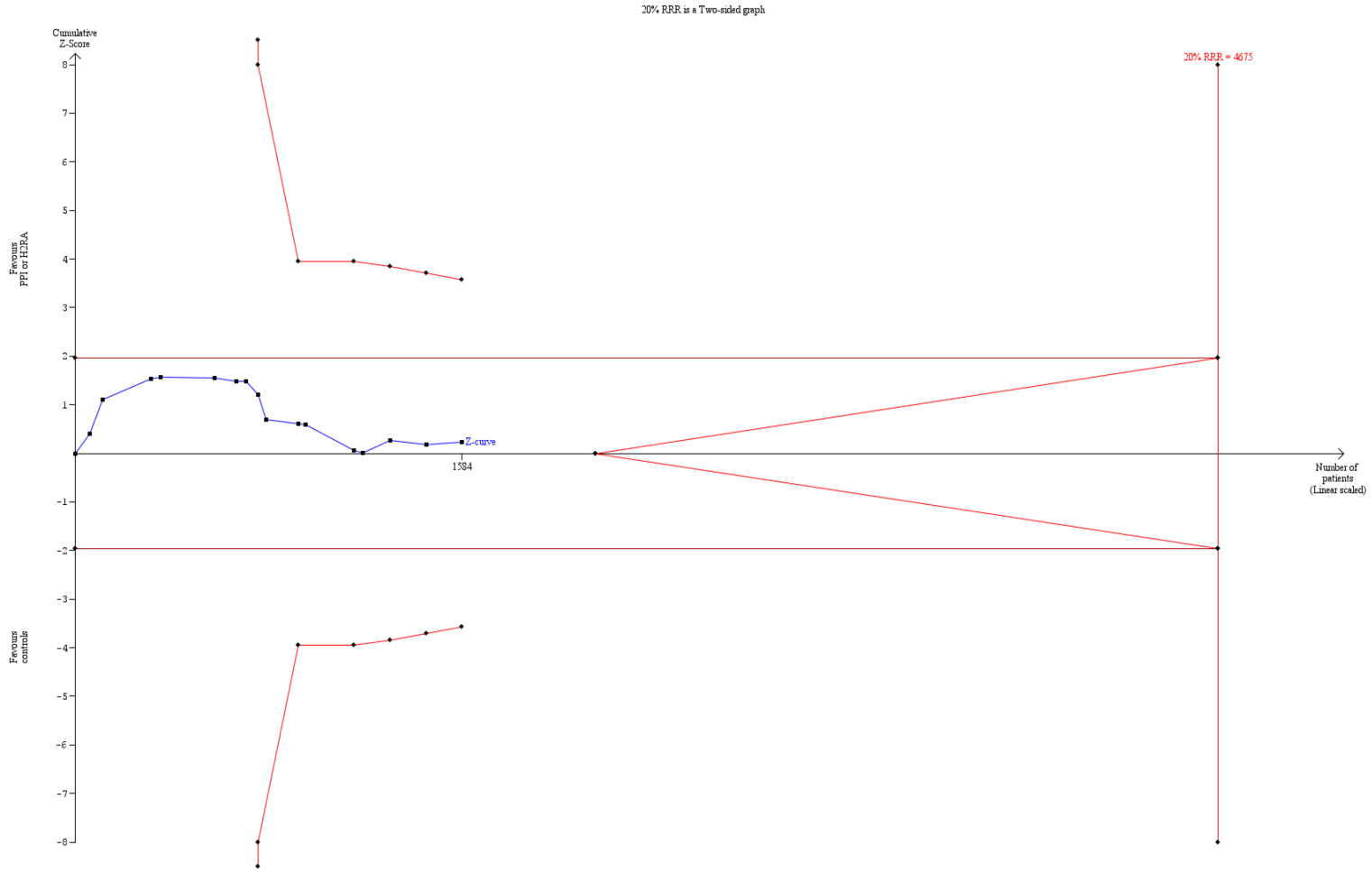
** Overt bleeding is defined as any episode of hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate in the ICU.

Clinically significant bleeding is defined as overt bleeding and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) [1, 5, 10] in the ICU

a. spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
b. start of vasopressor or a 20% increase in vasopressor dose
c. decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
d. transfusion of 2 units of packed red blood cells or more

Appendix 12. Trial sequential analysis of all-cause mortality (16 trials).

A diversity adjusted information size of 4,675 patients was calculated using α=0.05 (two sided), β=0.10 (power 90%), an anticipated diversity at the time when conclusive evidence has been reached (D^2=20%), an anticipated relative risk reduction of 20%, and an event proportion of 21% in the placebo/control arm. The blue cumulative z curve was constructed using a random effects model. The pooled effect is a RR=0.98 with a TSA adjusted 95% confidence interval of (0.75 to 1.28)



Appendix 13. International Committee of Medical Journal Editors (ICMJE) form for potential conflicts of interest.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name)
2. Surname (Last Name)
3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication.**

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

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Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

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Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial

<u>Final</u> protocol, version 3.0, incl. the following amendments (please find a summary of the changes at page 196):

1. August 2016: Appendix 7.1 Informed consent, Denmark
2. December 2016: Appendix 7.2 Informed consent, Denmark
3. June 2017: Appendix 3.1 Charter for the independent Data Monitoring and Safety Committee (DMSC)

Applicable protocol registration numbers:
EudraCT number: 2015-000318-24
ClinicalTrials.gov Identifier: NCT02467621

In drafting of present protocol Copenhagen Trial Unit's Standard Operating Procedures were used

Table of contents

Abstract

Background: Critically ill patients in the intensive care unit (ICU) are at risk of stress related gastrointestinal (GI) bleeding, and stress ulcer prophylaxis (SUP) is recommended. However, the evidence on SUP is of low quantity and quality, and studies have shown that proton pump inhibitors (PPI) may increase the risk of a number of serious adverse events.

Objectives: To assess the benefits and harms of SUP with PPI in adult, critically ill patients in the ICU.

Design: An investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of SUP with PPI versus placebo.

Inclusion and exclusion criteria: Inclusion criteria: Adult patients admitted to the ICU with one or more of the following acute conditions: shock, renal replacement therapy, mechanical ventilation expected to last > 24 hours, any kind of coagulopathy, treatment with anticoagulant drugs or liver disease. Exclusion criteria: contraindications to PPI, daily treatment with PPI and/or histamine-2-receptor antagonist, GI bleeding of any origin or known peptic ulcer during current hospital admission, organ transplant, withdrawal from active therapy or brain death, positive urine human chorionic gonadotropin (hCG) or plasma hCG or consent according to national regulations not obtainable.

Intervention: Experimental intervention is intravenous pantoprazole 40 mg daily. Control intervention is matching placebo (saline).

Outcomes: Primary outcome: Mortality 90 days after randomisation. Secondary outcomes: proportion of patients with clinically important GI bleeding, pneumonia, *Clostridium difficile* infection and myocardial ischemia, proportion of patients with clinically important GI bleeding, proportion of patients with pneumonia or *clostridium difficile infections*, 1 year mortality post-randomisation, days alive without organ support in the 90-day period, serious adverse reactions and a health economic analysis

Trial size: 2 x 1675 patients are required to show a 20% relative risk reduction or increase (5% absolute risk reduction or increase) in the primary outcome measure, assuming a baseline 90-day mortality of 25% (α=0.05 (two-sided), and β=0.1)

Time schedule:

2014 – November 2015: Governance approval applications, education of trial sites, other preparations

December 2015: First Danish patient enrolled

February 2015: Commencement of inclusion in other countries

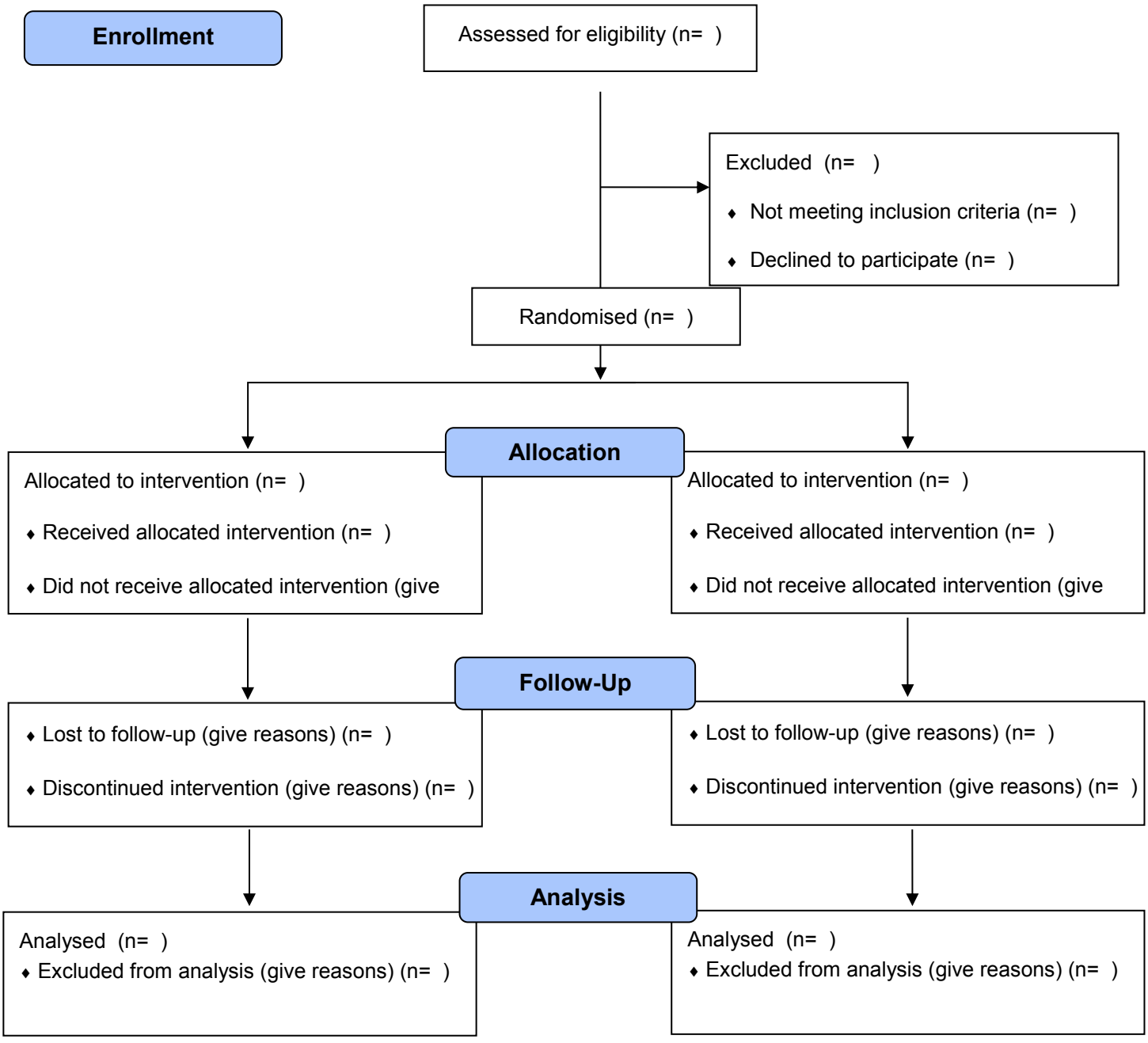
November 2017: Last patient enrolled

January 2018: Follow-up completed

May 2018: Data analysis and submission for publication

Trial flow chart

The flowchart (n=) will be filled in during or at the end of the trial.



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The research programme organisation is attached in *appendix* 1

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- Finland
- Iceland
- Italy
- Norway
- Switzerland
- The Netherlands
- United Kingdom

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List of abbreviations

AE	Adverse events
AIDS	Acquired Immune Deficiency Syndrome
AR	Adverse reactions
ARR	Absolute risk reduction
CDI	*Clostridium difficile* infection
CI	Confidence interval
CRIC	Centre for Research in Intensive Care
CRO	Contract research organisation
CT	Computed Tomography
CTSM	Clinical Trial Supply Management
DMSC	Data Monitoring and Safety Committee
eCRF	Electronic case report form
FiO2	Fractional inspired oxygen
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
GI	Gastrointestinal
H2RA	Histamine-2-receptor antagonist
hCG	Human Chorionic Gonadotropin
ICU	Intensive care unit
INR	International normalized ratio
MAR	Missing at random
MCAR	Missing completely at random
MNAR	Missing not at random
MR	Magnetic Resonance
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PaO2	Partial pressure of oxygen in arterial blood
PPI	Proton pump inhibitor
PT	Prothrombin time
RCT	Randomised clinical trial

RRI	Relative risk increase
RRR	Relative risk reduction
SAE	Serious adverse event
SAPS	Simplified Acute Physiology Score
SAR	Serious adverse reaction
SC	Steering Committee
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
SUP	Stress ulcer prophylaxis
SUSAR	Severe unexpected serious adverse reaction
TSA	Trial sequential analysis

1. Introduction and background

1.1 The patient population

Critically ill patients are at risk of stress-related gastrointestinal (GI) mucosal damage, which can progress to ulceration and GI bleeding [1]. Endoscopic studies have shown that gastric erosions are present in up to 90% of patients by the third day in the intensive care unit (ICU) [2, 3]. These lesions are in the vast majority of patients superficial and asymptomatic, but can progress and result in overt and clinically important bleeding [4]. Clinical important bleeding in the ICU is a serious condition, with an estimated 1-4 times increased risk of mortality and is associated with an excess length of ICU stay of 4-8 days [1].

Determining the incidence of GI bleeding in critically ill patients in the ICU is complicated by varying definitions of the outcome, difficulties in measuring the outcome, and different case mix. In randomised clinical trials (RCTs) and observational studies, the reported incidence of stress related GI bleeding among ICU patients ranges from 0.6-6.0% [1, 5–9]. Studies may have incorrectly included bleedings not related to stress ulcers e.g. oesophageal varices and ulcers already present upon ICU admission, e.g. undiagnosed peptic ulcers. In a prospective study by Cook *at al*. causes of haemorrhage were identified by endoscopy. Stress ulceration was defined as the sole source of bleeding in 14 of 30 patients [10]. Accordingly, sources of GI bleeding not prevented by stress ulcer prophylaxis (SUP) are frequent and the incidence of stress related ulcers may be lower than reported. Furthermore, diagnostics and treatment of critically ill patients in the ICU have improved considerably during the last decades [11, 12] and the incidence of stress ulcerations in critically ill patients may have changed.

1.2 Current treatment

Clinical trials have suggested a reduction in frequency of GI bleeding among ICU patients receiving SUP compared with patients receiving placebo or no prophylaxis [3, 13–19]. Based on this research conducted 20 years ago, SUP is recommended in international guidelines [20–23] and regarded as standard of care in the ICU. In a recent international unit evaluation 96 out of 97 units used SUP on a regular basis [24] and proton pump inhibitor (PPI) was used as first-line therapy in 66% of the participating ICUs [24].

The available PPIs are considered equally effective in the following comparative doses [25–29]:

Esomeprazole	10 mg

Lanzoprazole	15 mg
Omeprazole	10 mg
Pantoprazole	20 mg
Rabeprazole	10 mg

In 2014 Maclaren *et al*. published a retrospective cohort study with data from the Premier Perspective Database [30]. Patients aged 18 years or older requiring invasive mechanical ventilation and receiving either Histamine-2-receptor antagonist (H2RA) or PPI were scrutinized. Some 35,312 patients were included and among other findings the authors found that pantoprazole was the most frequently used PPI. This finding was confirmed in a cohort study from 2014, where pantoprazole was prescribed to 32% of patients treated with acid suppressants in the ICU [9].

1.3 Trial interventions

Because of the increased mortality and morbidity of ICU patients with clinically important GI bleeding, it is theoretically possible that PPIs reduce the risk of GI bleeding and hence the risk of death. However, research has not been able to confirm this and a 2014 observational study comprising more than 1,000 patients concludes that part of the increased mortality is explained by confounding [9]. A recent systematic review with meta-analysis and trial sequential analysis (TSA) assessed randomised trials comparing PPI or H2RA to placebo or no prophylaxis [31]. The review was conducted according to the Cochrane Handbook for Systematic Reviews [32] and included 20 trials with high risk of bias. The review results showed no significant difference between SUP and placebo/no prophylaxis on mortality and the TSA could exclude a 20% relative risk reduction or increase in mortality by using PPI or H2RA. Another meta-analysis from 2010 came to the same conclusion. Mortality was reported in 14 of the analysed trials and no significant reduction in mortality was found (OR 1.03, 95% CI 0.78-1.37; p=0.82).

Three RCTs have been conducted comparing PPI to placebo [33–35], but all had low sample size (n=169 [33], n=287 [34], and n=41 [35]) and neither of them were powered to show statistically significant differences in clinically relevant outcomes. The 2014 meta-analysis

comprised two of the trials (one was published after the meta-analysis) and concluded that the trials had a high risk of bias, and there were no differences in GI bleeding, pneumonia and mortality when comparing PPI to placebo.

PPI may reduce the risk of GI bleeding, but studies have indicated that they may also increase the risk of pneumonia, *Clostridium difficile* infection (CDI), acute myocardial ischemia, rhabdomyolysis, hypomagnesaemia and hypocalcaemia, and all of these conditions may increase the risk of death [36–39].

PPI versus H2RA

In recent years PPI has been considered the drug of choice in the management of most acid-related GI disorders [40]. The superior efficacy of PPIs over H2RAs has been demonstrated in various GI disorders, including peptic ulcer disease, gastroesophageal reflux disease and GI damage caused by non-steroidal anti-inflammatory drugs (NSAIDs) [40]. Randomised trials and meta-analyses have aimed to evaluate PPI compared to H2RA as SUP in the ICU. A recent published meta-analysis by Alhazzani et al. (14 trials, 1720 patients) compared PPI and H2RA [41]. The authors found that PPI was more efficient in reducing clinically important and overt GI bleeding, but no differences were shown regarding mortality, length of stay or pneumonia [41]. According to the authors the results were limited by sparse data, a difference between lower and higher quality trials, trial methodology and possible publication bias. Another systematic review and meta-analysis conducted in 2010 compared PPI and H2RA [42]. The study comprised seven RCTs and 936 ICU patients. The analysis did not find differences in rates of clinically important GI bleeding, pneumonia or death. Limitations of the review include limited number of patients, significant statistical heterogeneity, and risk of publication bias.

Clinical data on the control intervention

As described in previous section, studies have indicated that PPI is superior to H2RA to prevent clinically important and overt GI bleeding, but there is still a lack of quantitative and qualitative evidence for PPI being superior to placebo. Before comparing different SUP agents we need firm evidence of SUP being superior to placebo.

1.4 Adverse effects of PPI

Nosocomial pneumonia

Nosocomial infections are a significant in-hospital burden, and pneumonia is the most common nosocomial infection in the ICU, affecting 10–20% of patients receiving mechanical

ventilation for more than 48 hours [43]. It has been suggested that SUP agents may increase the frequency of nosocomial pneumonia and trials have investigated the incidence of pneumonia in patients treated with SUP compared to placebo/no prophylaxis [6, 17, 33, 34, 37, 44–46]. In 2004 Kantorova *et al.* found an insignificant difference in the incidence of pneumonia in patients treated with PPI/H2RA compared to placebo (n=287, 10%/9% vs. 7%). No meta-analysis of randomised trials have shown a statistically significant increased risk of nosocomial pneumonia when using SUP compared to placebo/no prophylaxis [31, 47].

Clostridium difficile infection

In recent years, concern has been raised that PPI increases the risk of CDI because host immunity is compromised by higher gastric pH [38, 48]. No randomised trials of SUP have reported the incidence of CDI in an ICU setting, but a recently published cohort study in adult critically ill patients requiring mechanical ventilation (n=35,312) found a 2-4 times increased risk of CDI in patients receiving PPIs compared to H2RAs [30]. Studies conducted outside the ICU demonstrate similar findings. In 2007 Leonard *et al.* found a significantly increased risk of CDI in non-ICU patients receiving H2RA or PPI, as compared to placebo [49] and a meta-analysis pooling 39 observational studies showed a significant association between PPI users and risk of developing CDI (OR 1.74, 95% CI 1.16-5.44) compared with non-users [50].

Acute myocardial ischemia

An association between use of PPIs and increased risk of cardiovascular events in patients receiving clopidogrel have been suggested [47, 51]. It may be that PPIs reduce the anti-platelet effects of clopidogrel, by interaction with the Cytochrome P450 enzyme complex in the liver [51]. In a case-control study of 18,130 clopidogrel users, use of co-existing PPI was associated with an increased risk of cardiovascular complications [51]. However, in the only RCT published, no cardiovascular interaction between clopidogrel and PPI was observed in non-ICU patients [42]. A cohort-study including 56,406 patients hospitalized for myocardial infarction or stroke, found an association between treatment with PPI and adverse cardiovascular outcomes after discharge regardless of treatment with clopidogrel [52].

In conclusion, valid evidence on the use of SUP in the ICU is lacking. Moreover, there is increasing concern about side-effects of SUP, in particular PPIs, but the data on side-effects are of very low quality.

1.5 Risks and benefits

Since PPI is a well-established drug and thousands of patients are treated with it every day, there will be no additional risk to patients receiving PPI. The risk will be limited to the known adverse reactions, including intolerance, abdominal pain and headache (*appendix* 2)
From the available evidence we do not know whether there will be a higher risk of GI bleeding, pneumonia, CDI, cardiovascular events or mortality in the PPI or placebo groups [31].

1.6 Ethical justification and trial rationale

As described in former sections, there is no firm evidence from systematic reviews of RCTs or single RCTs on the potential benefit or harm of PPIs in adult patients in the ICU. On the other hand, SUP is recommended in international guidelines [20–22], is regarded as standard of care and surveys have confirmed that PPI is already part of the treatment in ICUs worldwide. Since it is a widespread and currently used intervention [24], the patients assigned to the PPI group, will not be exposed to additional risk when enrolled in the trial. Any patient with known peptic ulcer or GI bleeding will be excluded and treated according to usual care. If a randomised patient develops upper GI bleeding and the clinician finds indication for treatment with PPI or H2RA, the trial intervention will be discontinued and the patient will be treated according to usual care. Therefore, patients in the control group will, presumably, also not be exposed to any additional risks.
Stress ulceration is a condition often seen in critically ill patients in the ICU. The majority of patients will be temporarily incompetent because of severe illness or as a consequence of the treatment (sedation). We cannot perform the trial randomising competent patients, because less sick (and thus competent) patients do not suffer from stress ulcers. Patients requiring acute treatment in the ICU e.g. mechanical ventilation are in an acute life-threatening condition and it would expose the patient to great risk not to initiate the necessary treatment in order to get informed consent. To make clinical trials with the goal of improving the outcome for ICU patients at risk of stress related GI bleeding, it is necessary to randomise and enrol patients before obtaining informed consent from the patient. Consent will be obtained according to national law, which in Denmark is by proxy (consent before randomisation by 2 doctors followed by next-of-kin and general practitioner/regional medical officer by health as soon as possible). The consenting party will be provided with written and oral information about the trial, so he/she is able to make an informed decision about participation in the trial. Written information and the consent form will be subjected to review and approval by the ethical

committee system according to national law in all participating countries. The consenting party can at any time, without further explanation, withdraw consent and data will be deleted if demanded.
The process leading to the achievement of consent may differ in the participating countries, but will be described and be in compliance with all applicable regulations in the country.
No biological material will be collected for the trial, thus no bio-bank will be formed.

1.6.1 Outcome considerations

It has been estimated that 39% of the patients receiving SUP in the ICU are discharged from the hospital with SUP without an obvious indication for continuation of therapy [53]. Besides the side effects described in former sections, long-term treatment with PPI is associated with several side effects e.g. an increased risk of fractures, hypomagnesaemia and rhabdomyolysis [36, 39], which may all have the potential to increase mortality. Assessing mortality as the primary outcome would give the opportunity to weigh the totality of benefits and harms of PPI. Furthermore the rationale for choice of outcomes is:

6. Mortality has not been the primary outcome of previous trials and we are sceptical that they got reliable information on mortality other than short term mortality (ICU/hospital) [31]
7. Nearly all previous trials assessing PPI or H2RA as SUP have had high risk of bias [31]. We know that high risk of bias trials tend to overestimate benefit and underestimate harm [54]. Accordingly, previous trial results might be biased and even though they seem to find a neutral effect on mortality this may be a biased estimate actually concealing excess mortality in the SUP groups
8. A meta-analysis of the previous trials did not reach a realistic information size so even neutral estimates may be misleading [31].
9. As a consequence of the 6S trial [55], where we found that bleeding was associated with death and that death where partly mediated by bleeding (and renal insufficiency), it appears odd that there should be a clinically significant reduction on GI bleeding (if PPI do prevent GI bleeding) without any effect on mortality [56].
10. A composite outcome of GI bleeding, pneumonia, CDI and acute myocardial ischemia seems valid to assess as well and will be a secondary outcome. The recommendation for using composite outcomes is reporting of the individual components as well, which will be done in a supplement to the primary publication.

Because of this and the potential to improve treatment of critically ill patients, the research question is in the public's interest. The design of the trial will minimise the risk of systematic errors and the trial will provide information on beneficial and/or harmful effects of using PPI as SUP.

1.6.2 Sample size considerations

It is difficult to produce reliable sample size estimations according to anticipated effects on GI bleeding because we have no reliable control groups due to the widespread use of PPI [57] and previous trials are in fact very old. As a consequence it has been necessary to calculate sample size estimations given that something may change if we stop/avoid PPI until GI bleeding actually happens (see *appendix* 11). The addressed intervention effect of 20% RRR or RRI on the primary outcome may seem high, but in a population with septic shock or in e.g. patients after cardiac arrest a 20% hazard ratio reduction corresponds to 1 months of extra median survival in patients with a median survival of approximately 5 months. So after all, a 20% RRR or RRI may not be as huge as could be anticipated, when it only results in a modestly longer survival in these patients. The power for even major effects on each of the possible side effects (pneumonia, CDI and acute myocardial ischemia) are small, but it will still be a large contribution to our knowledge on these outcomes that may seriously question, overthrow or confirm what we know so far. Furthermore, 3,350 patients included in one trial would be a huge contribution to the evidence, more than doubling the number of randomised patients and providing trial results with low risk of bias on mortality and serious adverse events.

No single trial, however big or well done, gives the final answer, and the SUP-ICU trial will not be an exception. However, the results will inform clinicians, guideline committee members and policy-makers on the use of PPI in the ICUs, as well as establish more (reliable) trust in PPI. Should we find 10-20% relative risk increase in mortality this will certainly trigger a new wave of trials on PPI or SUP in general and even though our trial may not be conclusive it may eventually lead to conclusions.

1.7 Trial conduct

The trial will be conducted in compliance with a published trial protocol, the Helsinki Declaration in its latest version [58], the good clinical practice (GCP) guidelines [59], and national laws in the participating countries. The protocol will be registered on

www.clinicaltrials.gov and at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) before trial start. No substantial deviation from the protocol will be implemented without prior review and approval of the regulatory authorities except where it may be necessary to eliminate an immediate hazard to the trial participants. In such case, the deviation will be reported to the authorities as soon as possible. Enrolment will start after approval by the ethical committees, medicines agencies, data protection agencies and health authorities in the participating countries. A manuscript with main points of the protocol including description of design, rationale and analysis plan will be submitted to a journal in English language.

2. Trial objectives and purpose

To assess the benefits and harms of PPI (pantoprazole) in adult, critically ill patients in the ICU.

3. Trial design

3.1 Trial design

An investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of pantoprazole versus placebo.

3.2 Randomisation

Patients will be screened for enrolment at admission to the ICU (see section 3.5). This will be ensured through implementation of trial methodology at trial sites.
1:1 randomisation will be centralised and web-based randomisation according to the computer-generated allocation sequence list, stratification variables (site and active hematologic cancer), and varying block size. The allocation sequence list will be unknown to the investigators to allow immediate and concealed allocation to intervention with pantoprazole or placebo. Each patient will be allocated a unique patient-screening number.

3.3 Blinding

Pantoprazole is preserved as a powder in a glass vial and needs to be dissolved in 10 ml of isotonic saline. The powder is momentarily dissolved with no need of shaking the vial. The solution is colourless and cannot be distinguished from saline. When the glass vial is masked,

it is not possible to determine whether the vial contains powder or is empty. The placebo will be an empty vial. Saline (10 ml) will be added to the empty vial in the same way as for the experimental intervention.
The blinding of the trial medication will be a white label covering the whole vial including the bottom and the neck. The label will contain the required information of the trial drugs. The top of the placebo vial will be identical with the vial of the active drug.
The allocated trial medication will be blinded to the clinical staff caring for the patient, to the patient, investigators, outcome assessors, and the data manager. The statistical analysis of the trial will be blinded with the intervention groups coded as, e.g., X and Y. Based on this blinded analysis two conclusions will be drawn: one assuming X is the experimental group and Y is the control group, and one conclusion assuming the opposite. Two abstracts will be written and accepted by the author group. After this, the blinding will be broken.

The members of the Data Monitoring and Safety Committee (DMSC) will remain blinded unless 1) they request otherwise or 2) one of the two interim analyses has provided strong indications of one intervention being beneficial or harmful (a charter for the independent DMSC is attached in *appendix* 3).

3.3.1 Unblinding

3.3.1.1 An individual
The intervention may be unblinded for individual patients if deemed necessary by the clinician or investigator for the treatment and safety of the patient.
In case of a suspected unexpected serious adverse reaction (SUSAR) the sponsor (or delegated party) shall break the blinding in order to judge the ‘expectedness’ and therefore the occurrence of a SUSAR (according to the summary of product characteristics), and report it to the authorities accordingly. See section 8 for more information.

3.3.1.2 Procedure
If the intervention for an individual patient needs to be unblinded during the trial, the treating physician shall contact Copenhagen Trial Unit (CTU), who will reveal the allocated trial intervention (pantoprazole or placebo). This can be done by telephone at all hours, any day of the week. If the investigator needs immediate unblinding of the trial medication, this can be done by removing the white label covering the glass vial.

3.5 Participant timeline

We will strive to enrol patients as soon as they fulfil the inclusion criteria. Patients will be allocated to either intravenous pantoprazole or placebo once daily and will continue the allocated intervention until death in the ICU or discharge from the ICU with a maximum of 90 days after randomisation.

If the patient is readmitted to the ICU within 90 days after randomisation the patient should continue the allocated treatment.

4. Selection of participants

All patients referred to a participating clinical trial site will be considered for participation. Patients will be eligible, if they fulfil all of the inclusion criteria and none of the exclusion criteria listed below (see also *appendix* 4)

4.1 Inclusion criteria

- Acute admission to the ICU **AND**
- Aged ≥ 18 years **AND**
- One or more of the following risk factors:
    - Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70 mmHg or lactate > 4 mmol/l)
    - Acute or chronic intermittent or continuous renal replacement therapy
    - Invasive mechanically ventilation which is expected to last > 24 hours. When in doubt of the forecast, the patient should be enrolled
    - Coagulopathy (platelets < 50 x 10^9/l or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds) documented within the last 24 hours
    - Ongoing treatment with anticoagulant drugs (prophylaxis doses excluded)
    - History of coagulopathy (platelets < 50 x 10^9/l or INR > 1.5 or PT > 20 seconds within 6 months prior to hospital admission
    - History of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history)

4.2 Exclusion criteria

- Contraindications to PPI
- Ongoing treatment with PPI and/or H2RA on a daily basis
- GI bleeding of any origin during current hospital admission
- Diagnosed with peptic ulcer during current hospital admission
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death
- Fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma-hCG
- Consent according to national regulations not obtainable

4.3 Participant discontinuation and withdrawal

4.3.1 Discontinuation and withdrawal at the choice of the participant

The procedure of handling withdrawal of consent from a patient will follow national regulations and will be described by each participating country.

The Danish procedure:
A patient, who no longer wishes to participate in the trial, can withdraw his/her consent at any time without need of further explanation, and without consequences for further treatment. Patients may be withdrawn from the trial at any time if consent is withdrawn by the person(s), who has given proxy-consent.
In order to limit the amount of missing data we plan to collect as much data from each patient as possible. Therefore, if possible, the investigator will ask the patient which aspects of the trial, he/she wishes to withdraw from:

- receiving the trial intervention only (allowing for all data registration and follow-up)

OR

- receiving the trial intervention AND further registration of daily data and/or follow-up

Only the patient can demand deletion of already registered data and only if the patient did not consent previously. If so, data will be deleted and a new patient will be randomised to obtain the full sample size.

4.3.2 Discontinuation and withdrawal at the choice of the investigator

A patient can be discontinued from the trial intervention by the investigator at any time, if:

- the patient experiences intolerable adverse reactions suspected to be related to the trial intervention

AND/OR

- the patient develops upper GI bleeding or another condition where the clinician finds indication for treatment with PPI or H2RA. The intervention will be stopped and the patient will receive relevant treatment.

In these cases, the collection of data will continue and the follow-up will be conducted. The patient will remain in the intention-to-treat population if the allocated trial intervention has been given.

If an ineligible patient is randomised by mistake and the trial intervention has not been given, data will be deleted (logged as a flawed randomisation) and a new patient will be randomised [60]. If the intervention has been given, the patient will continue in the trial and in the intention-to-treat population.

If the patient experiences a serious adverse reaction (SAR) or a suspected unexpected serious adverse reaction (SUSAR) the trial intervention will be stopped; data registration will continue (see section 8).

Patients who are transferred to another ICU will be regarded as discharged from the ICU unless the new ICU is an active SUP-ICU trial site. In any case, patients transferred to another ICU will be followed up for the primary outcome measure and as many of the secondary outcome measures as possible.

5. Selection and trial sites and personnel

5.1 Trial sites and setting

Trial sites will be ICUs [61] in Europe. Trial sites are listed in the section ‘Administrative information’. This section will be updated during the trial.

5.2 Trial personnel

All clinicians caring for patients in participating ICUs will be eligible to screen patients and perform the interventions.

All participating ICUs will receive written and oral instructions about the trial procedures. A 24-hour hotline will be available for questions.

6. Trial interventions

6.1 Experimental intervention

To ensure systemic uptake of pantoprazole all patients randomised to the experimental group will be given intravenous pantoprazole 40 mg upon randomisation and hereafter once daily. The intervention period will be from randomisation until discharge from the ICU or death in the ICU. If the patient is readmitted, the allocated intervention should be continued until final discharge from the ICU or the end of the 90-day trial period.

6.2 Control intervention

The control intervention will be placebo as described in section 3.3.
The intervention period will be identical to the intervention period of the experimental intervention.

6.3 Co-interventions

All patients in this trial will be offered co-interventions if indicated. Evidence regarding the use of sucralfate and antacids are weak [62] and we do not recommend the use of these drugs.

The registered co-interventions will be:

- any kind of mechanical ventilation (y/n) (daily)
- continuous treatment with vasopressor/inotropes (y/n) (daily)
- renal replacement therapy (y/n) (daily)
- number of units of red blood cells (daily)
- enteral nutrition (y/n) (daily)

ICU treatment and management in general will be at the discretion of the treating clinicians.

6.4 Concomitant interventions

PPI or H2RA cannot be prescribed as prophylaxis in the ICU during the intervention period. If the patient develops GI bleeding or another condition where treatment with one of the drugs is

indicted, the patient will be withdrawn from trial intervention and receive relevant treatment. Data collection will continue. If an included patient receives open-label PPI/H2RA (e.g. prescribed as prophylaxis) it will be considered a major protocol violation. This will be registered and the allocated trial intervention and data collection will be continued.

Previously randomised patients readmitted to the ICU:

- If the clinician finds indication to continue the PPI or H2RA prescribed in the ward, the trial medication will not be resumed, but data collection will continue
- If the clinician does not find indication to continue the PPI or H2RA prescribed in the ward, the drug will be discontinued and the allocated trial medication will be resumed

All other interventions will be allowed since they are expected to be distributed evenly in the two groups.

6.5 Intervention accountability

Pantoprazole for intravenous injection will be bought and delivered from Actavis to the Hospital Pharmacy of the Capital Region of Denmark. The pantoprazole will be part of the regular production and hence not made especially for the SUP-ICU trial. The Hospital Pharmacy will send it directly to Nomeco. Pharma-Skan ApS will produce the sterile empty vials used for placebo. The production will follow all regulations and according to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). The vials will be delivered to Nomeco CTSM who will be responsible for storage, blinding, packaging and distribution of vials with pantoprazole 40 mg and empty vials (placebo) to national and international trial sites. All services will be performed by qualified and trained personnel and according to GMP and GDP

A computer program (from CTU) will generate a coding list with numbers for the vials**.** At randomisation, the computer program will allocate vials from the specific trial site to the patient. Nomeco CTSM will be responsible for having a sufficient number of vials to be allocated to patients enrolled at each trial site. At each trial site, trial products will be stored in a secure place. Combined with the unique packaging and labelling number this will ensure that trial medications will not be mixed up with other medications. Used and unused products will be registered.

7. Outcomes

All outcomes are defined in *appendix* 4.

7.1 Primary outcome

90-day mortality post-randomisation

7.2 Secondary outcomes

- Proportion of patients with one or more of the following adverse events: clinically important GI bleeding, pneumonia, CDI, or acute myocardial ischemia in the ICU
- Proportion of patients with clinically important GI bleeding in the ICU
- Proportion of patients with one or more infectious adverse events (pneumonia or CDI) in the ICU
- 1-year "landmark" mortality post-randomisation
- Days alive without the use of mechanical ventilation, renal replacement therapy or circulatory support in the 90-day period
- Number of SARs as defined in a*ppendix* 4
- A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-benefit vs cost-minimisation analyses)

The specific elements of the composite outcomes will be reported in supplementary material to the primary publication.

7.3 Exploratory outcomes

No exploratory outcomes or sub-studies are planned. However, sub-studies will be encouraged as long as they don't hamper the completion of the main protocol and can be conducted after approval of the protocol by the Steering Committee (SC).

8. Safety

8.1 Definitions

Adverse event (AE): any undesirable medical event occurring to a patient during a clinical trial, which does not necessarily have a causal relationship with the intervention.

Adverse reaction (AR): any undesirable and unintended medical response related to the intervention occurring to a patient during a clinical trial. Adverse reactions are specified in the product characteristics of pantoprazole (see *appendix* 2 and 5)

Serious adverse event (SAE): any adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity.

Serious adverse reaction (SAR): any adverse reaction (as defined above) that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity.

Suspected unexpected serious adverse reaction (SUSAR): any suspected adverse reaction which is both serious and unexpected. SUSARs will be defined as serious reactions not described in the summaries of product characteristics for pantoprazole**.**

8.2 Risk and safety issues in the current trial

Pantoprazole is well tolerated and most adverse reactions have been mild and transient showing no consistent relationship with treatment. Approximately 5% of patients can be expected to experience adverse drug reactions. The most commonly reported are diarrhoea and headache, both occurring in approximately 1% of patients. Because of intravenous administration, there will be a risk of phlebitis in both groups.
In *appendix* 2 all adverse reactions for pantoprazole are listed.
Apart from the risk of phlebitis, there is no risk of adverse reactions to the placebo (10 ml of isotonic saline).
See Summary of Product Characteristics in *appendix* 5.

8.3 Serious adverse reactions and events

SARs to pantoprazole:
Registered SARs are defined in *appendix* 4 and ARs not registered are discussed in *appendix* 6.

SARs to 10 ml of isotonic saline:

No SARs are associated with such small amount of intravenous isotonic saline.

8.3.1 Recording of serious adverse reactions and events

SARs will be recorded daily in the eCRF from the time of the first administration of trial medication and until 24 hours after last administration of trial medication or the patient is discharged from the ICU. If the patient is readmitted to the ICU and trial medication is re-introduced, SARs will be recorded. When a SAR is registered in the eCRF the coordinating investigator will be informed directly which will secure fast reporting of SAR. SARs in the two groups will be compared in the interim analyses and as an outcome measure. If a patient experiences a SAR he or she will be withdrawn from the trial. Daily registration will be continued and the follow-up will be conducted.

If a patient experiences SUSAR, the local investigator must report this without undue delay to the Sponsor (or delegated party). The patient will be withdrawn from the trial and the trial medication will be demasked. If a SUSAR is still reasonable after demasking, a report will be conducted describing onset and end of event, severity, the relation to the intervention, the actions taken and the outcome.

SAEs will not be recorded as an entity, because the majority of ICU patients will experience several SAEs during their critical illness. The most important SAEs will be captured in the secondary outcome measures (days alive without life-support). Patient charts, notes and lab reports will contain daily registrations of clinical data, which can be obtained on request from the medical authorities.

8.4 Reporting

Trial investigators are to report SUSARs without any delay to the sponsor, which in turn will report these to the Danish Health and Medicine Authorities 7 days at the latest after the report has been received.

9. Procedures, assessments and data collection

9.1 Inclusion procedure

9.1.1 Screening

All patients admitted to participating ICUs will be eligible for screening. In fertile women a negative urine-hCG or plasma-hCG must be present before enrolment.

9.1.2 Procedures for informed consent

Patients will be enrolled after consent is obtained according to national regulations. This procedure will be described by each participating country. The procedure for Danish patients is described in *appendix* 7.

9.2 Data collection

9.2.1 Method

Data will be obtained in eCRFs from a combination of patient files and national registers. For patients transferred from a trial ICU to a non-trial ICU, data related to the outcomes of interest will be collected after transferral e.g. by national registers, phone calls, and patient charts.

9.2.2 Timing

Appendix 8 shows an overview of the timing and all variables are defined in *appendix* 4.

Baseline variables (not collected in the screening procedure)

- Sex
- Age at randomisation/date of birth
- Date of admission to hospital and date and time to ICU
- Elective or emergency surgery during current hospitalization (y/n)
- Treatment of suspected or confirmed CDI during current hospital admission (y/n)
- Treatment with NSAID or acetylsalicylic acid at hospital admission (y/n)
- Treatment with anticoagulants at hospital admission (y/n)
- Intravenous thrombolysis within the previous 3 days (y/n)
- Co-morbidities (see definitions in *appendix* 4):
    - history of chronic lung disease
    - history of myocardial ischemia
    - history of severe chronic heart failure (NYHA 3-4)

    - history of chronic renal failure in the last year prior to hospital admission
    - treatment with at least 0.3 mg/kg/day of prednisolone equivalent for at least one month in the 6 month prior to ICU admission
    - active hematologic cancer
    - metastatic carcinoma
    - AIDS
- Values for simplified acute physiology score (SAPS) II 24 hours prior to randomisation (not covered above): heart rate, systolic blood pressure, core temperature, PaO2/ FiO2 ratio, urinary output, urea, white blood cell count, potassium, sodium, bicarbonate, bilirubin, Glasgow Coma Scale (GCS) score (*appendix* 9)
- Variables for severity organ failure assessment (SOFA) scoring 24 hours prior to randomisation not covered in SAPS II scoring: blood platelets, MAP, dose of noradrenalin, adrenalin and dopamine, use of inotropes, plasma creatinine (*appendix* 10)

Daily during ICU admission:

- Delivery of trial medication (y/n)
- Open label treatment with PPI/H2RA (y/n)
- Invasive or non-invasive mechanical ventilation (y/n)
- Circulatory support (infusion of vasopressor/inotropes) (y/n)
- Any form of renal replacement therapy (y/n)
- Onset of pneumonia (as defined in *appendix* 4) on this day (y/n)
- Treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, or enteral fidaxomicin) for suspected or proven CDI on this day (y/n)
- Acute myocardial ischemia (as defined in *appendix* 4) on this day (y/n)
- Enteral feeding on this day (y/n)
- Number of units of RBCs
- Overt bleeding episodes (hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate) (y/n)
- SARs (y/n) (*appendix* 4)

Bleeding form (only for patients with overt bleeding)

- Data on clinically important bleeding (overt GI bleeding as defined above and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) in the ICU:
    - a spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
    - start of vasopressor or a 20% increase in vasopressor dose
    - decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
    - transfusion of 2 units of packed red blood cells or more
- Origin of GI bleeding confirmed (y/n)
- Verification of ulcer/gastritis/esophageal varices (y/n)
- Haemostasis achieved/attempted by endoscopy/open surgery/coiling (y/n)

Follow-up 90 days after randomisation

- Death (y/n, if yes, date of death)

Follow-up 1 year after randomisation

- Death (y/n, if yes, date of death)

10. Data handling and record keeping

10.1 Data management

Data will be entered into an electronically, web-based eCRF from medical files and national registers by trial personnel.

10.2 Confidentiality

Each patient will receive a unique trial identification number. Trial investigators will receive personal username and passwords to access the randomisation system and the eCRF. Each site will only have access to site specific data.

Data will be handled according to the National Data Protection Agency, and is protected by the Danish national laws ‘Loven om behandling af personoplysninger’ and ‘Sundhedsloven’.

10.3 Biobanking

No biobank will be formed.

10.4 Access to data

All original records (incl. consent forms, eCRFs, and relevant correspondences) will be archived at trial sites for 15 years. The clean electronic trial database file will be delivered to the Danish Data Archive and maintained for 15 years and anonymised if requested by the authorities.

11. Statistical analysis

90-day mortality and 1-year mortality have been chosen as outcomes for all-cause mortality. Besides landmark mortality, mortality 90 days and 1 year after last randomised patient have been considered, but due to practical and organisational matters, and lack of centralised registration, it will be difficult and for some countries impossible to get mortality data up to 3 years after enrolment of a patient.

11.1 Sample size estimation and power calculations

11.1.1 Sample size estimation for the primary outcome

Primary outcome measure

Assuming a baseline 90-day mortality of 25% [9] (see *appendix* 11) α=0.05 (two-sided), and β=0.1, 3350 patients (2 x 1675) will be needed to show a 20% relative risk reduction (RRR) or increase (RRI) corresponding to a 5% absolute risk reduction or risk increase in the primary outcome measure.

Trial Sequential Analysis [63, 64] of existing trials (n=16) has showed that 35% (1584 patients) of the required information size to detect or reject a 20% RRR corresponding to 4,575 patients has been accrued [31]. Consequently, there is an information gap of around 3000 patients assuming a 20% RRR in mortality (*appendix* 12). With the inclusion of an additional 3350 patients it is expected that the pooled effect will cross the boundary for benefit/harm or the boundary for futility.

11.1.2 Power estimations for secondary outcomes

Power estimations are based on 3350 included patients, a risk of type 1 error of 5%, and a minimal clinically relevant difference as stated:

Clinically important GI bleeding: 46% power (baseline 3% -> 2% = 33% RRR) for showing or discarding a numbers-needed-to-treat (NNT) of 100.
Pneumonia: 85% power (baseline 20% -> 16% = 20% RRR) for showing or discarding a NNT of 25.
CDI: 53% power (baseline 10% -> 8% = 20% RRR) for showing or discarding a NNT of 50.
Myocardial ischemia: 29% power (baseline 5% -> 4% = 20% RRR) for showing or discarding a NNT of 100

11.2 Statistical methods

The primary analysis will be conducted including the intention-to-treat population [65–67]. A sensitivity analysis will be conducted including the per-protocol population, excluding patients with a major protocol violation (patients who did not receive the allocated trial intervention at all, patients who did not receive the trial intervention for at least two days in a row, treatment with PPI or H2RA without clinically indication and withdrawal from trial intervention). Patients transferred to another ICU will be considered discharged from the ICU.
The primary analysis of all dichotomous outcomes will compare the outcome at 90 days after randomisation in the two groups by binary logistic regression analysis with adjustment for stratification variables [68]: site and active haematological cancer
A secondary analysis will be performed adjusting for stratification variables together with other known major prognostic co-variates: age, baseline SOFA score, and type of admission (medical, elective surgery or emergency surgery).
Further details will be provided in a statistical analysis plan.

11.2.1 Pre-planned subgroup analyses

We will compare the primary outcome measure in pre-specified subgroups defined according to 1) shock at randomisation (y/n), 2) mechanical ventilation at randomisation (y/n), 3) coagulopathy at randomisation or history of coagulopathy (y/n), 4) history of liver disease (y/n) 5) type of ICU admission (medical/surgery) and 6) SAPS II > 53 points (y/n).

11.2.2 Significance

A two-sided P value of less than 0.05 will be considered statistically significant.

11.2.3 Interim analysis

Interim analyses will be conducted after patient no. 1650 and 2500 has been followed for 90 days.

The DMSC will constitute its own plan of monitoring and meetings. The charter for the independent Data Monitoring and Safety Committee (DMSC) (*appendix* 3) defines the minimum of obligations and primary responsibilities of the DMSC as perceived by the SC, its relationship with other trial components, its membership, and the purpose and timing of its meetings.

The DMSC may recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function [69]. If an analysis of the interim data from 1650/2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the SC may stop the trial [67]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 15% RRR will not be an option as intervention effects less than 15% RRR of all-cause mortality may be clinically relevant as well.

11.2.4 Early stopping criteria

See previous section

11.2.5 Accountability procedure for missing data/population for analysis

If less than 5% of data are missing on any primary or secondary outcome, a complete case analysis without input of missing values will be performed. If missing data are more than 5%, a blinded statistician will assess whether data are 'missing completely at random' (MCAR criterion) based on a rational assessment of the pattern of missing data [70]. Little's test will be used if there remains doubt [71]. If it is concluded that data are not 'missing completely at random', multiple imputation using chained equations will be performed by creating ten input data sets under the assumption that the data are missing data at random (MAR criterion) [72, 73]. We will use outcomes and the most important baseline characteristics in the multiple imputation. The exact variables to be used to estimate the missing values will be outlined in

the detailed statistical analysis plan: If multiple imputation is used, then the primary result of the trial will be based on these data. The unadjusted, non-imputed analysis will also be made available. If multiple imputation is used, we use a best-worst worst-best case scenario as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the 'best-worst-case' scenario it is assumed that all patients lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived, had no serious adverse reactions etc.); and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived; have had a serious adverse reaction etc.). Conversely, in the 'worst-best-case' scenario, it is assumed that all patients who were lost to follow up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome. When continuous outcomes are used, a 'beneficial outcome' will be defined as the group mean plus two standard deviations (SD) of the group mean, and a 'harmful outcome' will be defined as the group mean minus two SD of the group mean.

12. Quality control and quality assurance

The coordinating investigator will be responsible for organizing the trial sites including education of local investigators, research nurses, and other trial site personnel before the initiation of the trial. This education will be continuously documented and two annual investigator meetings will be planned.

After initiation, trial site investigators will be responsible for all trial-related procedures at their site, including education of staff in trial-related procedures, recruitment and follow-up of patients and entry of data. Clinical staff at the trial sites will be responsible for the treatment of trial patients.

12.1 Monitoring of the intervention groups

The trial will be externally monitored following a monitoring plan developed in collaboration with the GCP Unit in Copenhagen, which will coordinate the monitoring done by local GCP units and/or monitors in all countries. A centralised day-to-day monitoring of the eCRF will be done by the coordinating investigator or her delegates.

13. Legal and organisational aspects

13.1 Finance

13.1.1 Trial funding

The SUP-ICU trial is funded by the Innovation Fund Denmark (4108-00011A). The funding sources will have no influence on trial design, trial conduct, data handling, data analysis or publication.

13.1.2 Compensation

Trial sites will be given DKR 1500 (200 EUR) in case money for each patient with 90-day follow-up to compensate for the increased workload participation infers.

13.2 Insurance

In Denmark, all trial participants are insured by the Patient Insurance Association. Patient insurance will be ensured before initiating the trial in each participating countries. Costs for insurance will be sought financed by funding.

13.3 Plan for publication, authorship and dissemination

13.3.1 Publication and authorship

The trial will be registered on www.clinicaltrials.gov. The final protocol will be published as a design and rationale paper including the plan for analyses. Upon trial completion the main manuscript with trial results whether positive, negative or neutral will be submitted for a peer-reviewed publication, to one of the major clinical journals. Furthermore the results will be published at the SUP-ICU home page (www.sup-icu.com).

The listing of authors will be as follows: M Krag will be the first author, A Perner the second, J Wetterslev the third, M Wise will be the fourth author and the next authors will be the national investigators according to the number of included patients per country, then the trial statistician and trial site investigators dependent on the number of included patients per site. MH Møller will be the last and corresponding author, and 'the SUP-ICU trial co-authors' will be written.

The SC will grant authorship depending on personal input according to the Vancouver definitions. If a trial site investigator is to gain authorship, the site has to include 50 patients or

more. If the site includes 100 patients or more, two authorships will be granted per trial site, 150 patients will give 3 authorships per trial site and so on.
The DMSC and investigators not qualifying for authorship will be acknowledged with their names under the “SUP-ICU Trial investigators’ in an *appendix* to the final manuscript.
Funding sources will have no influence on data handling or analyses or writing of the manuscript.

13.4 Spin-off projects

Spin-off projects will be encouraged and conducted when approved by the SC. Presently no spin-off projects have been developed.

13.5 Intellectual property rights

Sponsor and primary investigator is MH Møller. Therefore no contract on intellectual property rights is indicated. The initiative for the SUP-ICU trial has been taken by MH Møller and A Perner and by doctors at multiple ICUs, none of whom have affiliations to institutions that may have economic interests in the trial results. Contracts between national investigators and Sponsor and between site investigators and Sponsor will be signed before conduct of the trial.

13.6 Organisational framework

The trial is part of the SUP-ICU research programme (www.sup-icu.com) and Centre for Research in Intensive Care (CRIC).

13.7 Trial timeline

2014 – November 2015: Governance approval applications, education of trial sites, other preparations
December 2015: First Danish patient enrolled
February 2015: Commencement of inclusion in other countries
November 2017: Last patient enrolled
January 2018: Follow-up completed
May 2018: Data analysis and submission for publication

14. Appendix

Appendix 1: Research Programme Organisation

15. References

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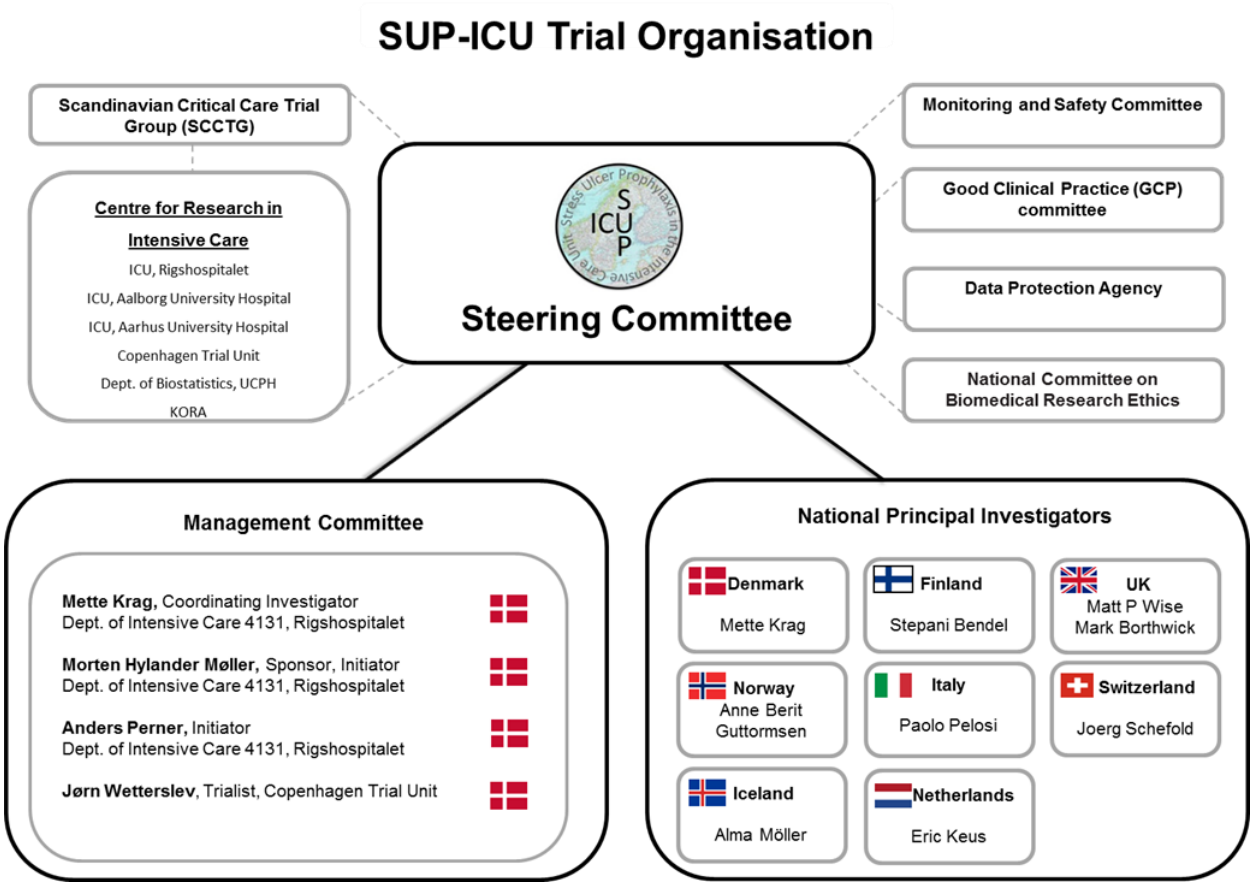
Appendix 1. Trial organisation



Appendix 2. Undesirable effects of pantoprazole

Approximately 5% of patients can be expected to experience adverse drug reactions. The most commonly reported adverse drug reactions are diarrhoea and headache, both occurring in approximately 1% of patients.
For all adverse reactions reported from post-marketing experience, it is not possible to apply any adverse reaction frequency and therefore they are mentioned with a “not known” frequency.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency **System Organ Class**	**Common***	**Uncommon***	**Rare***	**Very rare***	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombo-cytopenia; Leukopenia Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemi as and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia (see section 4.4) Hypocalcaemia in association with hypomagnesemia; Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorien-tation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)

Nervous system disorders		Headache Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision / blurred vision		
Gastrointestinal disorders		Diarrhoea; Nausea / vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort			
Hepatobiliary disorders		Liver enzymes increased (transaminas-es, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash / exanthema / eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Ery-thema multiforme; Photosensitivity
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

*Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Appendix 3. Charter for the independent Data Monitoring and Safety Committee (DMSC)

ClinicalTrials.gov Identifier: NCT02467621
Research ethical committee no: H-15003141

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the steering committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the SUP-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of patients, their management, improving adherence to protocol-specified regimens and retention of patients, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC is planned by protocol to meet physically in order to evaluate the planned interim analyses of the SUP-ICU trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC (to be announced). The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail in order to discuss the safety for trial participants. The sponsor has the responsibility to report the overall number of Serious Adverse Reactions (SARs) yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions if suggested by the data, see section on ‘closed sessions’. The recommendations of the DMSC regarding stopping,

continuing or changing the design of the trial should be communicated without delay to the SC of the SUP-ICU trial. As fast as possible, and no later than 48 hours, the SC has the responsibility to inform all investigators of the trial and all the sites including patients in the trial, about the recommendation of the DMSC and the SC decision hereof.

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The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.
The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the SC will appoint the replacement(s).

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Two formal interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-day follow-up data of 1650 (approximately 50% of sample size estimation) and 2500 (approximately 75% of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC.

At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC membership who generates the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the SC.

Closed reports will include analysis of the primary outcome measure. In addition, analyses of the secondary outcome measures and SARs will also be reported. These closed reports will be prepared by independent biostatistician being a member of the DMSC, with assistance from the trial data manager, in a manner that allow them to remain blinded.

The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within two months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be provided available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician being a member of the DMSC will prepare these open reports in co-operation with the trial data manager.

The reports should be provided to DMSC members approximately three days prior to the date of the meeting.

Minutes of the DMSC Meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the SC to continue, hold or terminate the trial.

Interim analyses will be conducted after patient no. 1650 and 2500 has been followed for 90 days. The DMSC will recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function [69]. If an analysis of the interim data from 1650/2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial [67]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an intervention effect of 15% RRR will not be

an option as intervention effects less than 15% RRR of all-cause mortality may be clinically relevant as well.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The SC is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the protocol. For the two intervention groups, the DMSC will evaluate data on:

<u>The primary outcome measure</u>

Mortality 90 days after randomisation of each patient ("landmark mortality").

<u>The secondary outcome measures</u>

- Proportion of patients with one or more of the following adverse events: clinically important gastrointestinal (GI) bleeding, pneumoni, *clostridium difficile* infection (CDI), and acute myocardial ischemia
- Proportion of patients with clinically important GI bleeding
- 1 year mortality post-randomisation
- The occurrence of SARs in the ICU

The DMSC will be provided with these data from the coordinating centre as:

Number of patients randomised

Number of patients randomised per intervention group

Number of patients stratified pr. stratification variable per intervention group

Number of events, according to the outcomes, in the two groups

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

DMSC should yearly be informed about SARs occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power, if protocol specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the Coordinating Centre to the DMSC
The DMSC will be provided with a file containing the data defined as follows:

Row 1 contains the names of the variables (to be defined below).

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The values of the following variables should be included in the database:

8. screening_id: a number that uniquely identifies the patient

9. rand_code: The randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received

10. clin_imp_bleed: clinically important GI bleeding (1 if the patient had one or more episodes and 0 if the patient did not)

11. pneumonia: onset of pneumonia in the ICU after randomisation (1 = one or more episodes, 0= no episodes)

12. clostridium: *clostridium difficile* infection (1 = one or more episodes, 0= no episodes)

13. ami: acute myocardial ischemia in the ICU (1 = one or more episodes, 0= no episodes)

14. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SARs)

Appendix 3.1 Charter for the independent Data Monitoring and Safety Committee (DMSC) (Amendment 3):

Amendment to the previously approved protocol entitled 'Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial', version 3.0, October 20th 2015. EudraCT 2015-000318-24.

This amendment replaces Appendix 3 in the above mentioned protocol.

Amendment June 23, 2017

Cancelation of the second interim analysis (2500/3350 included patients).

Due to the high inclusion rate, the SUP-ICU trial Steering Committee and Data Monitoring and Safety Committee (DMSC) has decided to cancel the second interim analysis as the results (incl. 90-day follow-up) will not be available until the trial has been completed.

The statement paper from the DMSC following the first interim analysis (1675/3350 included patients) supports this decision. The wording in the trial protocol, including appendix 3 has not been revised.

ClinicalTrials.gov Identifier: NCT02467621

Research ethical committee no: H-15003141

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived of the steering committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the SUP-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of patients, their

management, improving adherence to protocol-specified regimens and retention of patients, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

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20. ami: acute myocardial ischemia in the ICU (1 = one or more episodes, 0= no episodes)

21. SAR_indic: SAR indicator (1 = one or more SARs, 0 = no SARs)

Appendix 4. Definitions

Definition of stratification variables

Site: all participating intensive care units (ICUs) will be assigned a number identifying the department.

Haematological malignancy includes any of the following:

- leukemia: Acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL).
- lymphoma: Hodgkin's disease, Non-Hodgkin lymphoma (e.g. small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), hairy cell leukemia (HCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), post-transplant lymphoproliferative disorder (PTLD), T-cell prolymphocytic leukemia (T-PLL), B-cell prolymphocytic leukemia (B-PLL), Waldenström's macroglobulinemia, other NK- or T-cell lymphomas
- Multiple myeloma/plasma cell myeloma

Definition of inclusion criteria

Acute admission to the ICU: a non-planned admission. It does not include planned recovery after surgery or similar planned admissions. ICU admission does not include admissions to semi intensive care, intermediate intensive care or similar beds.

Age: the age of the patient in whole years at the time of randomisation. The age will be calculated from date of birth

Shock: at least one of the following:

- systolic pressure < 90 mmHg
- mean arterial pressure < 70 mmHg
- use of vasopressors or inotropes (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosimendan)
- lactate > 4 mmol/l

Renal replacement therapy: acute or chronic intermittent or continuous renal replacement therapy

Patients with expected duration of invasive mechanically ventilation > 24 hours: the treating clinician estimates that the patient will be invasively mechanically ventilated for more than 24 hours. When in doubt of this forecast the patient should be enrolled

Coagulopathy: platelets < 50 x 10^9/l or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds documented within the last 24 hours

Treatment with anticoagulant drugs: ongoing treatment with: Dipyridamole, vitamin K antagonists, ADP-receptor inhibitors, therapeutic doses of low molecular weight heparin, new oral anticoagulant drugs, intravenous direct thrombin (II) inhibitors and similar drugs. Acetylsalicylic acid (all doses) and low molecular weight heparin in prophylactic doses are NOT included

History of coagulopathy: coagulopathy defined as platelets < 50 x 10^9/l AND/OR INR > 1.5 AND/OR PT > 20 seconds within 6 months prior to hospital admission.

History of chronic liver disease: portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history

Definition of exclusion criteria

Contraindications to proton pump inhibitors (PPI): any history of intolerance to PPI or additives or treatment with atazanavir (HIV medication)

Ongoing treatment with PPI and/or histamine-2-receptor antagonists (H2RA): ongoing is defined as treatment <u>not</u> being discontinued at ICU admission. If clinicians do not find indication for continuation of treatment with PPI/H2RA during ICU stay, the patient will be eligible for inclusion.

GI bleeding during current hospital admission: GI bleeding of any origin (both upper and lower) documented in the patient charts

Peptic ulcer: peptic ulcer confirmed by endoscopy or other method during current hospital admission

Organ transplant: any kind of organ transplant during current hospital admission.

Withdrawal from active therapy or brain death: patients where withdrawal or brain death is documented in the patient charts

Known pregnancy: fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma-hCG

Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain necessary consent before inclusion of the patient according to the national regulations

Definition of baseline variables

Sex: the genotypic sex of the patient

Age: defined in inclusion criteria

Date of admission to hospital: the date of admission to the first hospital the patient was admitted to during the current hospital admission

Elective surgery: surgery during current hospital admission scheduled 24 hours or latter in advance

Emergency surgery: surgery during current hospital admission that was added to the operating room schedule 24 hours or less prior to surgery

Medical admission: when no surgery has been performed during current hospital admission OR surgery has been performed more than 1 week prior to ICU admission

Treatment with anticoagulants at hospital admission and at ICU admission: anticoagulants are defined in inclusion criteria

Treatment with non-steroidal anti-inflammatory drugs (NSAID) and acetylsalicylic acid at hospital admission: treatment with all doses of these drugs at hospital admission

Treatment with intravenous thrombolysis: treatment with all kinds of intravenous thrombolysis within 3 days prior to randomisation

Coagulopathy: defined in inclusion criteria

Treatment of suspected or confirmed *Clostridium difficile* infection (CDI) during current hospital admission

Coexisting illness must have been present in the past medical history prior to ICU admission and are defined as follows:

- Chronic lung disease: chronic obstructive pulmonary disease (COPD), asthma or other chronic lung disease or treatment with any relevant drug indicating this at admission to hospital
- Previous myocardial infarction: history of myocardial infarction
- Chronic heart failure: New York Heart Association Functional Class (NYHA) III-IV. NYHA III: The patient has marked limitations in physical activity due to symptoms (fatigue, palpitation or dyspnoea) even during less than ordinary activity (walking short distances 20-100 m. or walking up stairs to 1st floor). The patient is only comfortable at rest. NYHA class 4: The patient is not able to carry out any physical activity (without discomfort (fatigue, palpitation or dyspnoea). Symptoms are present even at rest and the patient is mostly bedbound
- History of chronic renal failure: need of any form of chronic renal replacement therapy within the last year
- Liver disease: defined in baseline variables
- History of coagulopathy: defined in baseline variables
- Immunosuppression: patients treated with at least 0,3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission
- Metastatic cancer: proven metastasis by surgery, CT scan or any other method
- Hematologic malignancy: defined as stratification variable
- AIDS: HIV positive patients with one or more HIV defining diseases such as pneumocystis jerovechii pneumonia, Kaposi's sarcoma, Lymphoma, tuberculosis or toxoplasma infection

The Simplified Acute Physiology Score (SAPS II) [74] (*appendix* 9) is based on the most extreme (highest or lowest) values from 24 hours prior to randomisation. The score consists of 17 variables: 12 physiologic variables, age, type of admission and 3 variables related to underlying disease to give a total score ranging from 0 to 163, with higher scores indicating greater severity of illness. The score will be calculated from data from the 24 hours prior to randomisation

The Sequential Organ Failure Assessment (SOFA) Score [75] (*appendix* 10) will be calculated from raw physiology and treatment data from the 24 hours prior to randomisation. The SOFA Score consists of weightings for six organ systems to give a total score ranging from 0 to 24, with higher scores indicating a greater degree of organ failure.

Definition of daily collected variables:
Delivery of trial medication: confirmation of administration of the trial drug

Treatment with PPI or H2RA: prescription of any of these drugs in any dose (major protocol violation if the treatment is initiated (e.g. as prophylaxis) without clinical indication (e.g. gastrointestinal bleeding)

Mechanical ventilation: invasive and non-invasive mechanical ventilation including continuous mask CPAP or CPAP via a tracheotomy. Intermittent CPAP is NOT mechanical ventilation.

Circulatory support: continuous infusion of vasopressor or inotrope (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosimendan)

Renal replacement therapy: any form of renal replacement therapy on this day. In patients receiving intermittent renal replacement therapy days between treatments are included

Clinically important GI bleeding, onset of pneumonia, CDI, and acute myocardial ischemia in the ICU are defined as outcomes

Treatment with enteral feeding: any dose of enteral feeding (including oral nutritional intake) during the day

Units of red blood cells: cumulated number of units of red blood cells transfused during the day

Serious adverse reactions (SARs) are defined below

Definition of bleeding variables:
Confirmed diagnosis: diagnosis/origin of bleeding confirmed by endoscopy or other method

Verification of ulcer/gastritis/bleeding oesophageal varices: confirmation of one of the three specific diagnoses by endoscopy or other method

Haemostasis achieved or attempted: documentation in patient charts of haemostasis achieved or attempted by endoscopy, open surgery or coiling

Definitions of outcome measures

Primary outcome:

90-day mortality: death from any cause within 90 days following the day of randomisation

Secondary outcomes:

Proportion of patients with one or more of the following adverse events: clinically important GI bleeding, pneumonia, CDI, and acute myocardial ischemia. The events are defined as follows:

Clinically important GI bleeding: overt GI bleeding* and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) in the ICU

e) spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
f) start of vasopressor or a 20% increase in vasopressor dose
g) decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
h) transfusion of 2 units of packed red blood cells or more

*Overt GI bleeding: hematemesis, coffee ground emesis, melena, haematochezia or bloody nasogastric aspirate

Pneumonia: episodes of newly confirmed pneumonia according to the modified CDC criteria [76]

- Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):
  1. new or progressive and persistent infiltrate
  2. consolidation
  3. cavitation

- AND at least one of the following:
  1. fever (>38°C) with no other recognised cause
  2. leukopenia (white cell count < 4 x 109/l) or leucocytosis (white cell count >12 x 109/l)
- AND at least two of the following

5. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements
6. new onset or worsening cough, or dyspnoea, or tachypnoea
7. rales or bronchial breath sounds
8. worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand)

CDI: Treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, enteral fidaxomicin) for suspected or proven CDI

Acute myocardial ischemia: ST-elevation myocardial infarction, non-ST elevation myocardial infarction or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischemic signs on ECG and clinical presentation) AND receiving treatment as a consequence of this (reperfusion strategies (PCI/thrombolysis) or initiation/increased antithrombotic treatment)

Proportions of patients with clinically important GI bleeding: proportion of patients with one or more episodes of clinically important GI bleeding as defined above

Proportion of patients with one or more infectious adverse events: proportion of patients with one or more episodes of pneumonia or CDI

1-year mortality: landmark mortality 1 year post-randomisation

Duration of life support in the ICU: the number of days alive and free from respiratory or circulatory support and of renal replacement therapy as defined below. The outcome will be days alive without use of mechanical ventilation, circulatory support or renal replacement therapy in the 90-day period, and will be defined as the percentage of days without mechanical ventilation, circulatory support and renal replacement therapy (as defined in daily collected variables) in the 90 days after randomisation

Serious adverse reactions: number of serious adverse reactions as defined below

The elements of all composite outcomes will be reported in the supplementary material

A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-benefit vs cost-minimisation analyses).

Definitions of serious adverse reactions

A serious adverse reaction (SAR) is defined as any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity.

Patients will be monitored for onset of SARs occurring between the first dose of trial medication and until discharge from the ICU. If a patient is withdrawn from the trial intervention, SARs will be recorded for 24 hours after the last dose of trial medication or discharge from ICU. If the patient is readmitted to the ICU and trial intervention is reintroduced, data collection for SARs will be resumed. If a patient experiences a SAR the patient will be withdrawn from the trial intervention but data collection and follow-up will be continued (see section 4.3.2)

SARs will be defined as follows:

Anaphylactic reactions defined as urticaria and at least one of the following

- Worsened circulation (>20% decrease in blood pressure or >20% increase in vasopressor dose)
- Increased airway resistance (>20% increase in the peak pressure on the ventilation)
- Clinical stridor or bronchospasm
- Subsequent treatment with bronchodilators

Agranulocytosis is defined as any new, acute and severe drop in granulocytes to $< 0.5 \times 10^9/l$ requiring active monitoring or treatment

Pancytopenia is defined as any new, severe drop in red blood cells, white blood cells and platelets requiring active monitoring or treatment

Acute hepatic failure is defined as severe and progressing hepatic failure as judged by the treating doctor or the investigator

Steven-Johnson syndrome and toxic epidermal necrolysis are defined as severe dermatological reactions with a skin biopsy confirming the diagnosis

Interstitial nephritis is defined as a nephritis affecting the interstitium of the kidneys surrounding the tubules with a kidney biopsy confirming the diagnosis

Angioedema (Quincke's oedema) is defined as a vascular reaction involving the deep dermis, subcutaneous or submucosal tissues, resulting in a characteristic localized oedema.

Adverse reactions not registered will be discussed in *appendix* 6.

Appendix 5. Translation of the Danish summary of product characteristics

SUMMARY OF PRODUCT CHARACTERISTICS

for

Pantoprazol “Actavis”, powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazol “Actavis” 40 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 40 mg of pantoprazole (as sodium sesquihydrate)

Excipients with known effect:
Each vial contains 5.0 mg of sodium citrate dihydrate and sodium hydroxide q.s.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially “sodium free”.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White or almost white, uniform porous cake.

For the solution reconstituted with 10 ml of 0.9% NaCl solution the pH is approximately 10 and the osmolality is approximately 382 mOsm/Kg

For the solution reconstituted with a further 100 ml of 0.9% NaCl solution or 5% glucose solution the pH is approximately 9 and 8.5, respectively

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Reflux oesophagitis
- Gastric and duodenal ulcer
- Zollinger – Ellison Syndrome and other pathological hypersecretory conditions.

4.2 Posology and method of administration

This medicine should be administered by a healthcare professional and under appropriate medical supervision.

The intravenous administration of pantoprazole is recommended only if oral application is not appropriate. Data are available on intravenous use for up to 7 days. Therefore as soon as oral therapy is possible, treatment with pantoprazole i.v. should be discontinued and 40 mg pantoprazole p.o. should be administered instead.

Posology

Gastric and duodenal ulcer, reflux oesophagitis
The recommended intravenous dose is one vial of pantoprazole (40 mg) per day.

Zollinger-Ellison Syndrome and other pathological hypersecretory conditions
For the long-term management of Zollinger-Ellison Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg of pantoprazole i.v. Thereafter, the dosage can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

In case a rapid acid control is required, a starting dose of 2 x 80 mg of pantoprazole i.v. is sufficient to manage a decrease of acid output into the target range (<10 mEq/h) within one hour in the majority of patients.

Special populations
Paediatric population
The experience in children is limited. Therefore, pantoprazole i.v. is not recommended for use in patients below 18 years of age until further data become available.

Hepatic impairment:
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section 4.4).

Renal impairment:
No dose adjustment is necessary in patients with impaired renal function.

Elderly
No dose adjustment is necessary in elderly patients.

Method of administration
A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. For instructions for preparation see section 6.6. The prepared solution may be administered directly or may be administered after mixing it with 100 ml of 9 mg/ml (0.9%) sodium chloride injection, or 50 mg/ml glucose (5%) solution for injection.

After preparation the solution must be used within 12 hours (see section 6.3).

The medicinal product should be administered intravenously over 2 – 15 minutes.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In presence of alarm symptoms
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Hepatic impairment

In patients with severe liver impairment, the liver enzymes should be monitored during therapy. In the case of a rise in the liver enzymes, the treatment should be discontinued (see section 4.2).

Co-administration with atazanavir
Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria (e.g. *Salmonella* and *Campylobacter* and *C.difficile*).

Sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pantoprazole on the absorption of other medicinal products
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependant bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicines such as erlotinib.

HIV medications (atazanavir)
Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon or warfarin)
Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

Other interactions studies
Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with drugs also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Breast-feeding
Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

4.7 Effects on ability to drive and use machines

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1% of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (<1/10,000 to <1/1,000), very rare (1/10,000) not known (cannot be estimated from the available data). For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency / **System organ class**	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders			Agranulocytosis	Thrombo-Cytopenia; Leukopenia; Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemia and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaemia; Hypocalcaemia in association with hypomagnesaemia; Hypokalaemia

Frequency / System organ class	Common	Uncommon	Rare	Very rare	Not known
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination: Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders		Headache; Dizziness	Taste disorders		Paraesthesia
Eye disorders			Disturbances in vision/blurred vision		
Gastrointestinal disorders		Diarrhoea; Nausea/ vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort.			
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders		Rash/ exanthema/ eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photo-sensitivity
Musculo-skeletal and connective tissue disorders			Arthralgia; Myalgia		Muscle spasm as a consequence of electrolyte disturbances
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombo-phlebitis	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

There are no known symptoms of overdose in man.
Systemic exposure with up to 240 mg administered intravenously over 2 minutes was well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable.

In case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors, ATC code: A02BC02.

Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H^+/K^+-ATPase enzyme i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

The fasting gastrin values increase under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see section 5.3) have not been observed in humans.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid according to results in animal studies.

5.2 Pharmacokinetic properties

General Pharmacokinetics
Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Distribution
Pantoprazole's plasma protein binding is about 98%. Volume of distribution is about 0.15 l/kg.

Elimination

The substance is almost exclusively metabolised in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathways include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. There were few cases of subjects with delayed elimination. Because of specific binding of pantoprazole to the proton pumps of the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole; the rest are excreted in the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole.

Characteristics in patients/special groups of subjects:
Approximately 3% of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60%. These findings have no implications for the posology of pantoprazole.

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (2-3 hours), excretion is still rapid and thus accumulation does not occur.
Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

A slight increase in AUC and C_{max} in elderly volunteers compared with younger counterparts is also not clinically relevant.

Paediatric population
Following administration of single intravenous doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

5.3 Preclinical safety data

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment. In the two-year rodent studies an increased number of liver tumours was observed in rats and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg). The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at does above 5 mg/kg. Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium citrate dihydrate

Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale: 3 years

After reconstitution, or reconstitution and dilution, chemical and physical in-use stability has been demonstrated for 12 hours at 25ºC. The reconstituted, or reconstituted and diluted medicinal product should not be refrigerated.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the vial in the outer carton to protect from light.
For storage conditions of the reconstituted and diluted medicinal product see section 6.3.

6.5 Nature and contents of container

15 ml, type I, colourless glass vial, sealed with a grey chlorobutyl stopper and an aluminium flip-off cap, containing 40 mg pantoprazole powder for solution for injection.

Pack sizes: 1, 5, 10 and 20 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A ready-to-use intravenous solution is prepared by injecting 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection into the vial containing the lyophilised powder. The reconstituted solution should be clear and colourless. This solution may be administered directly or may be administered after mixing it with 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Glass or plastic containers should be used for dilution

Pantoprazol “Actavis” 40 mg powder for solution for injection should not be prepared or mixed with solvents other than those stated.

This medicine should be administered intravenously over 2- 15 minutes.

The content of the vial is for single use only. Any product that has remained in the container or the visual appearance of which has changed (e.g. if cloudiness or precipitation is observed) should be disposed of in accordance with local requirements.

Appendix 6. Adverse reactions not registered

Thrombocytopenia will not be registered as a serious adverse reaction (SAR) since it is a frequent condition among critically ill patients and is a part of the inclusion criteria (coagulopathy).

Increased plasma levels of bilirubin, (jaundice) and liver enzymes (hepatocellular injury) is not registered as they in themselves are not considered serious conditions. The potential serious consequence hepatic failure will be registered daily as a SAR.

Hyponatremia, hypokalaemia, hypomagnesaemia and hypocalcaemia will not be registered as electrolyte disturbances as they are frequent among ICU patients. These conditions are monitored and treated daily in all ICU patients. According to the summary of product characteristics, hypomagnesaemia will not be relevant until treatment for at least three months and in most cases one year.

Leukopenia will not be registered. Reduced white blood cell counts are frequent among ICU patients and can be associated with many different systemic or hematological disorders in critically ill patients.

Renal and urinary disorders will not be registered as they are not considered serious conditions in themselves, but the potential serious consequence will be reflected in the outcome measure days alive without use of renal replacement therapy.

The following possible adverse reactions will not be registered as SARs as they are not considered serious conditions:

Hyperlipidaemia, lipid increases, weight changes, taste disorders
Sleep disorders, depression, disorientation, hallucination, confusion, headache, dizziness
Paraesthesia, blurred vision
Nausea, vomiting, abdominal distension, constipation, dry mouth, abdominal pain and discomfort
Rash, exanthema, pruritus, erythema multiforme, photosensitivity, urticarial, hypersensitivity
Arthralgia, myalgia, asthenia, fatigue and malaise
Reproductive system, breast disorders, gynecomastia
Injection site thrombophlebitis
Body temperature increased

Oedema peripheral

Fracture of the hip, wrist or spine (treatment > 1 year)

Appendix 7. Informed consent, Denmark

In Denmark temporarily incompetent patients will be enrolled after informed consent from two physicians, who are independent of the trial (trial guardians). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and general practitioner or the Regional Medical Officer of Health according to Danish law. Patients, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

Lack of informed consent from the general practitioner
If the general practitioner does not want to make up his/her mind about the patient's participation in the trial, e.g. if he/she does not have the knowledge to make the decision or for any other reasons the patient will continue in the trial until informed consent can be obtained from the patient him-/herself. If the general practitioner cannot be reached the Regional Medical Officer of Health will be contacted for consent.

Lack of informed consent from the patient's next of kin
If it is not possible (i.e. contact cannot be obtained) - after obtaining informed consent from two independent physicians and from the patient's general practitioner/the Regional Medical Officer of Health - to obtain informed consent from the patient's next of kin, the patient will continue in the trial until informed consent can be obtained from the patient him-/herself.

Lack of informed consent from the patient's next of kin and the patient deceases
If it is not possible (i.e. contact cannot be obtained) - after obtaining informed consent from two independent physicians and from the patient's general practitioner/the Regional Medical Officer of Health - to obtain informed consent from the patient's next of kin, the patient will continue in the trial until informed consent can be obtained from the patient him-/herself. If the patient deceases before informed consent is obtained, or remains in a permanent state of incompetence, the collected data will be kept and trial outcomes will be collected centrally.

Deviation from the standard informed consent

According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the specific patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

Appendix 7.1 Informed consent, Denmark (Amendment 1):

Amendment to the previously approved protocol entitled 'Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial', version 3.0, October 20th 2015

This amendment replaces Appendix 7 in the above mentioned protocol.

In Denmark temporarily incompetent patients will be enrolled after informed consent from one physician, who is independent of the trial (trial guardians). As soon as possible after enrolment, consent will be obtained from the patient's next of kin. Patients, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

Lack of informed consent from the patient's next of kin
If information about the patient's next of kin is not available after inclusion the investigator will seek information from e.g. the patient's general practitioner, the police, nursing homes etc. In these situations it may take 1-2 weeks to conclude that no next of kin can be identified. If no one is identified and the patient remains incompetent the trial intervention will be discontinued. All initiatives to identify the patient's next of kin will be documented in patient files, logs or similar.

Lack of informed consent from the patient's next of kin and the patient deceases
If the patient deceases before informed consent has been obtained (due to rapid progression of critical illness or because the patient's next of kin is not yet identified) and the patients has been correctly included in the trial, collected data will be kept for analysis.

Deviation from the standard informed consent
According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected during the trial. However, the purpose of this trial is not to generate new knowledge about the

specific patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

Appendix 7.2 Informed consent, Denmark (Amendment 2):

Amendment to the previously approved protocol entitled 'Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial', version 3.0, October 20th 2015

This amendment replaces amendment 7.1 to the above mentioned protocol.

In Denmark temporarily incompetent patients will be enrolled after informed consent from one physician, who is independent of the trial (first trial guardian). As soon as possible after enrolment, consent will be obtained from the patient's next of kin and a second physician (second trial guardian). The second trial guardian must be different from the first trial guardian, but also independent of the trial. Patients, who regain consciousness, will be asked for informed consent as soon as possible. The process leading to the achievement of informed consent will be in compliance with all applicable regulations. The consenting party will be provided with written and oral information about the trial so he/she is able to make an informed decision about participation in the trial. The information will be given in a separate room, and the consenting party has the right to bring a companion.
Written information and the consent form will be subjected to review and approval by the relevant ethic committees.

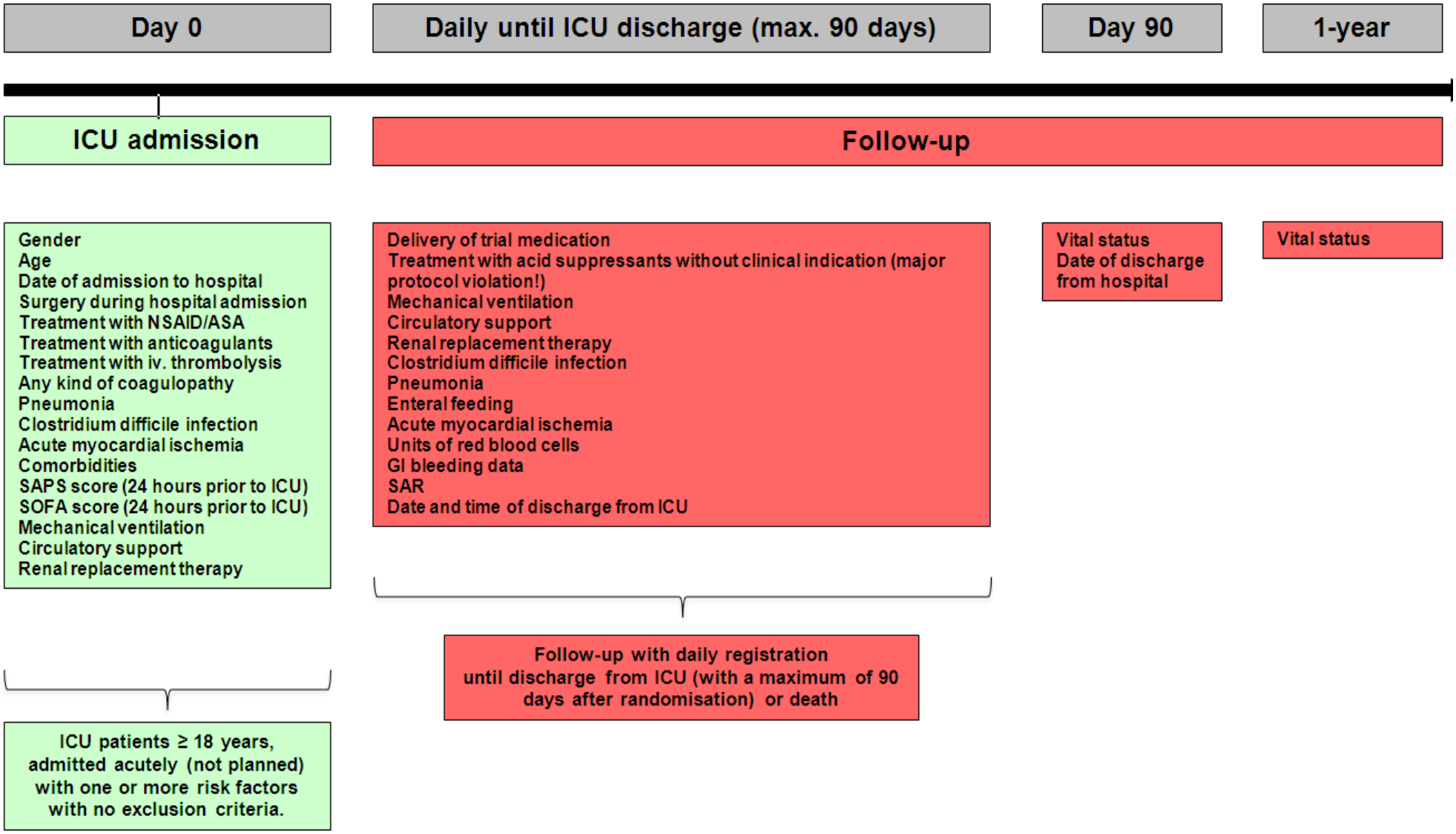
Lack of informed consent from the patient's next of kin
If information about the patient's next of kin is not available after inclusion the investigator will seek information from e.g. the patient's general practitioner, the police, nursing homes etc. In these situations it may take 1-2 weeks to conclude that no next of kin can be identified. If no one is identified and the patient remains incompetent the trial intervention will be discontinued. All initiatives to identify the patient's next of kin will be documented in patient files, logs or similar.

Lack of informed consent from the patient's next of kin and the patient deceases
If the patient deceases before informed consent has been obtained (due to rapid progression of critical illness or because the patient's next of kin is not yet identified) and the patient has been correctly included in the trial, collected data will be kept for analysis.

Deviation from the standard informed consent
According to the standard informed consent form from the National Ethics Committee regarding competent patients, the patient can choose not to receive information about the data collected

during the trial. However, the purpose of this trial is not to generate new knowledge about the specific patient, so we find that this question is redundant, and have omitted the question from the consent form to spare the patient from making unnecessary decisions.

Appendix 8. Timeline



Appendix 9. SAPS II scoring sheet [74]

Part 1

Variable	Points:	26	13	12	11	9	7	6	5	4	3	2	0
Age													< 40
Heart rate					< 40							40-69	70-119
Systolic blood pressure mmHg			< 70						70-99				100-199
Body temperature													
°C													< 39
°F													<102.2
Only if ventilated													
PaO_2 mmHg/FiO_2					< 100	100-199		≥200					
PaO_2 kPa/FiO_2					<13.3	13.3-26.5		≥26.6					
Urinary output ml/day					<500					500-999			> 1000
Serum urea level													
mmol/l													< 10.0
(g/dl)													(< 0.6)
WBC				<1.0									1.0-19.9
10^9/l													
Serum potassium											<3.0		3.0-4.9
mmol/l													
Serum sodium mmol/l									<125				125-144
Serum bicarbonate mEq/l									<15		15-19		≥20
Bilirubin													
umol/l													< 68.4
(mg/dl)													(<4.0)
Glascow coma scale score	<6		6-8				9-10		11-13				14-15
Chronic disease													
Type of admission													Scheduled surgical

Part 2

Variable	1	2	3	4	6	7	8	9	10	12	15	16	17	18
Age						40-59				60-69	70-74	75-79		≥80
Heart rate				120-159		≥160								
Systolic blood pressure mmHg		≥200												
Body temperature °C °F			≥39.0 ≥102.2											
Only if ventilated PaO_2 mmHg/FiO_2 PaO_2 kPa/FiO_2														
Urinary output ml/day														
Serum urea level mmol/l (g/dl)					10.0-29.9 0.60-1.79				≥30.0 ≥1.80					
WBC 10^9/l			≥20.0											
Serum potassium mmol/l			≥5.0											
Serum sodium mmol/l	≥145													
Serum bicarbonate mEq/l														
Bilirubin umol/l (mg/dl)				68.4-102.5 (4.0-5.9)				≥102.6 (≥6.0)						
GCS score														
Chronic disease								Metastatic cancer	Hematologic malignancy				AIDS	
Type of admission					Medical		Unsceduled surgical							
Sum of points														

Appendix 10. SOFA score [75]

	0	1	2	3	4
Respiraiton					
PaO_2/FiO_2					
(mmHg)	≥ 400	< 400	< 300*	< 200†	< 100†
(KPa)	≥ 53	< 53	< 40*	< 27†	< 13†
Coagulation					
Platelets (x 10^3/mm3)	≥ 150	101-150	51-100	21-50	≤ 20
Liver					
Bilirubin					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
(umol/l)	< 20	20-32	33-101	102-204	> 204
Cardiovascular					
Hypotension*			Dopamine ≤ 5☼ **OR**	Dopamine ≥ 5☼ **OR**	Dopamine > 15☼ **OR**
(MAP)	≥ 70	< 70	Dobutamine (any dose) **OR**	Norepinephrine ≤ 0.1☼ **OR**	Norepinephrine > 0.1☼ **OR**
			Milrirone (any dose) **OR**	Adrenaline ≤ 0.1☼ **OR**	Adrenaline > 0.1☼
			Levosimendan (any dose) **OR**	Vasopression (any dose) **OR**	
				Phenylephrine (any dose) **OR**	
CNS					
Glascow coma scale score	15	13-14	10-12	6-9	< 6
Renal					
Creatinine					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(umol/l)	< 110	110-170	171-299	300-440	>440
OR					
Urine output				<500 ml/day	<200 ml/day

* without respiratory support
† with respiratory support
☼Adrenergic agents administered for at least one hour (doses given are in ug/kg/min).

Appendix 11. Power estimation

All power estimations have been calculated on data from the international SUP-ICU 7-day inception cohort study[57].
Since we do not know whether treatment with acid suppressants reduce or increase mortality, a number of scenarios have been considered (+/- 20 relative risk reduction):

1) 25.0% mortality 90 days after inclusion among patients with:
At least one risk factor*
No acid suppressants at ICU admission
Treatment with acid suppressants during ICU admission
No clinically important bleeding** during ICU admission

Power estimations:

ARR	Power	Patients per group
- 5%	80%	1091
	90%	1461
+ 5%	80%	1248
	90%	1671

We do not know whether PPI benefits or harms the patients, and need to include both scenarios. With 1671 patients in each group we will be able to show an absolute increase in risk of 5% with 90% power at the primary outcome, but also an absolute risk reduction of 5% with 90% power. The sample size has been calculated on patients fulfilling inclusion and exclusion criteria in the SUP-ICU trial and because few patients were not treated with acid suppressants during ICU admission, the estimation is based on the group receiving acid suppressants (intervention group)

2) 25.9% mortality 90 days after inclusion among patients with:
At least one risk factor*
No acid suppressants at ICU admission
Treatment with acid suppressants during ICU admission
Bleeding (overt or clinically important**) or no bleeding during ICU admission

Power estimations:

ARR	Power	Patients per group
- 5,2%	80%	1034
	90%	1384
+5,2%	80%	1180
	90%	1579

3) 29.2% mortality 90 days after inclusion among patients with:

At least one risk factor*

Acid suppressants and no acid suppressants at ICU admission

Treatment with acid suppressants during ICU admission

No bleeding (overt or clinically important**) during ICU admission

Power estimations:

ARR	Power	Patients per group
- 5,8%	80%	901
	90%	1206
+5,8%	80%	1014
	90%	1357

4) 30.5% mortality 90 days after inclusion among patients with:

At least one risk factor*

Acid suppressants or no acid suppressants at ICU admission

Treatment with acid suppressants during ICU admission

Bleeding (overt or clinically important**) or no bleeding during ICU admission

Power estimations:

ARR	Power	Patients per group
- 6,1%	80%	837
	90%	1120
+6,1%	80%	937
	90%	1254

*Risk factors are: shock, renal replacement therapy, coagulopathy and coagulopathy and liver disease as comorbidities)

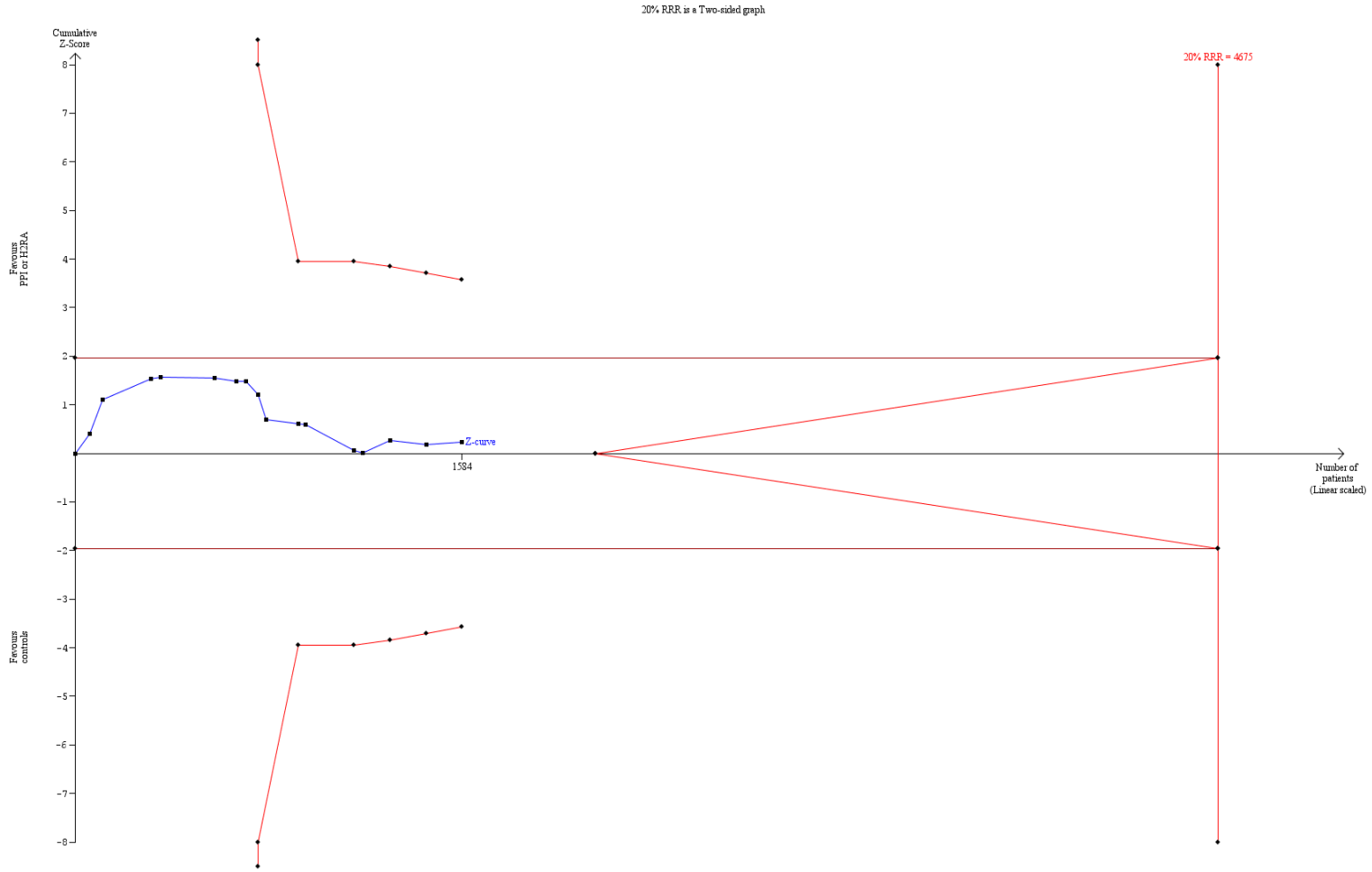
** Overt bleeding is defined as any episode of hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate in the ICU.

Clinically significant bleeding is defined as overt bleeding and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) [1, 5, 10] in the ICU

e. spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
f. start of vasopressor or a 20% increase in vasopressor dose
g. decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
h. transfusion of 2 units of packed red blood cells or more

Appendix 12. Trial sequential analysis of all-cause mortality (16 trials).

A diversity adjusted information size of 4,675 patients was calculated using α=0.05 (two sided), β=0.10 (power 90%), an anticipated diversity at the time when conclusive evidence has been reached (D^2=20%), an anticipated relative risk reduction of 20%, and an event proportion of 21% in the placebo/control arm. The blue cumulative z curve was constructed using a random effects model. The pooled effect is a RR=0.98 with a TSA adjusted 95% confidence interval of (0.75 to 1.28)



Appendix 13. International Committee of Medical Journal Editors (ICMJE) form for potential conflicts of interest.

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

SAVE

ICMJE Form for Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Intellectual Property.

This section asks about patents and copyrights, whether pending, issued, licensed and/or receiving royalties.

5. Relationships not covered above.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

Definitions.

Entity: government agency, foundation, commercial sponsor, academic institution, etc.
Grant: A grant from an entity, generally [but not always] paid to your organization
Personal Fees: Monies paid to you for services rendered, generally honoraria, royalties, or fees for consulting , lectures, speakers bureaus, expert testimony, employment, or other affiliations
Non-Financial Support: Examples include drugs/equipment supplied by the entity, travel paid by the entity, writing assistance, administrative support, etc.
Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
Issued: The patent has been issued by the agency
Licensed: The patent has been licensed to an entity, whether earning royalties or not
Royalties: Funds are coming in to you or your institution due to your patent

1

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name) | 2. Surname (Last Name) | 3. Date

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title

6. Manuscript Identifying Number (if you know it)

Section 2. The Work Under Consideration for Publication

Did you or your institution **at any time** receive payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were **present during the 36 months prior to publication.**

Are there any relevant conflicts of interest? ☐ Yes ☐ No

ADD

Section 4. Intellectual Property -- Patents & Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☐ No

ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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ICMJE Form for Disclosure of Potential Conflicts of Interest

Section 5. Relationships not covered above

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ Yes, the following relationships/conditions/circumstances are present (explain below):

☐ No other relationships/conditions/circumstances that present a potential conflict of interest

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Section 6. Disclosure Statement

Based on the above disclosures, this form will automatically generate a disclosure statement, which will appear in the box below.

Generate Disclosure Statement

Evaluation and Feedback

Please visit http://www.icmje.org/cgi-bin/feedback to provide feedback on your experience with completing this form.

Summary of changes to the original protocol

Amendments to the previously approved protocol entitled 'Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit: A randomised, blinded, placebo-controlled trial', version 3.0, October 20th, 2015.

Amendment 1 (August 2016)
Appendix 7.1 Informed consent, Denmark
This amendment replaces Appendix 7 in the above-mentioned protocol.
Description: New legislation on informed consent in Denmark.

Amendment 2 (December 2016)
Appendix 7.2 Informed consent, Denmark
This amendment replaces Appendix 7.1 in the above-mentioned protocol.
Description: New legislation on informed consent in Denmark.

Amendment 3 (June 2017)
Appendix 3.1 Charter for the independent Data Monitoring and Safety Committee (DMSC)
This amendment replaces Appendix 3 in the above-mentioned protocol.
Description: Cancelation of the second interim analysis (2500/3350 included patients). Due to the inclusion rate the SUP-ICU trial Steering Committee, in full agreement with the DMSC, has decided to cancel the second interim analysis as the results (incl. 90-day follow-up) would be available only after the inclusion of the last trial patient.
The statement paper from the DMSC following the first interim analysis (1675/3350 included patients) supports this decision. The decision has been approved by relevant Danish authorities.

Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial: detailed statistical analysis plan

Comprehensive details of the SUP-ICU trial has been published elsewhere.[1] This statistical analysis plan was prepared before randomisation of patients and data collection in the SUP-ICU trial was completed. The analysis plan was approved by the SUP-ICU Steering Committee on September 22, 2016. Analysis of data for the primary publication will be conducted according to this plan.

Randomisation

Thirty-one sites in Denmark, Finland, the Netherlands, Switzerland and Norway are currently screening and randomising patients in the SUP-ICU trial. Some additional, 5-10 ICUs from the United Kingdom, Italy and Denmark are expected to participate. Copenhagen Trial Unit (CTU)[21] is responsible for centralised and web-based 1:1 randomisation according to a computer-generated allocation sequence list, with two stratification variables (site and active hematologic cancer), and varying block size.

Blinding

The allocated trial medication will be masked to clinical staff caring for the patient, to the patient, investigators and outcome assessors. The statistical analysis of the trial will be blinded with the intervention groups coded as, e.g., X and Y. Based on this blinded analysis two conclusions will be drawn: one assuming X is the experimental group and Y is the control group, and another assuming the opposite. Two abstracts will be written and accepted by the SUP-ICU Steering Committee. After this, the intervention groups will be unmasked.

Sample size

Because of the widespread use of SUP, no reliable control group for sample size estimation is available and producing reliable sample size estimations according to anticipated effects on GI bleeding is difficult.[1] As a consequence it has been necessary to calculate sample size estimations given that something may change if we withhold PPI until GI bleeding actually happens. Assuming a baseline 90-day mortality of 25%,[2] α=0.05 (two-sided), and β=0.1, 3350 patients (2 x 1675) will be needed to show a 20% relative risk reduction (RRR) or increase (RRI) corresponding to a 5% absolute risk reduction or increase in the primary outcome measure. Trial Sequential Analysis[22,23] of existing trials (n=16) has showed that 35% (1584 patients) of the required information size to

detect or reject a 20% RRR or RRI corresponding to 4575 patients has been accrued.[8] Consequently, there is at least an information gap of around 3000 patients taking a 20% RRR in mortality as a clinically relevant effect size.

Outcome measures

Primary outcome

The primary outcome measure is all-cause mortality within 90 days after randomisation.

Secondary outcomes

1. Proportion of patients with one or more episodes of clinically important GI bleeding, pneumonia, *Clostridium difficile* infection or myocardial ischemia. The events are defined in appendix 1
2. Proportion of patients with one or more episodes of clinically important GI bleeding
3. Proportion of patients with one or more infectious adverse events (pneumonia or *Clostridium difficile* infections)
4. All-cause mortality within 1 year after randomisation
5. Percentage of days alive without use of life support (mechanical ventilation, circulatory support or renal replacement therapy) in the 90-day period
6. The number of patients with one or more serious adverse reactions (SARs) (defined in appendix 2)
7. A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified prior to the analysis.

Pre-planned subgroup analyses

The primary outcome measure will be compared in the following pre-specified subgroups (definitions provided in appendix 2)

1. Shock at randomisation (y/n) (a hypothesised increased intervention effect in patients with shock at randomisation)
2. Mechanical ventilation at randomisation (y/n) (a hypothesised increased intervention effect in patients mechanically ventilated at randomisation)
3. Coagulopathy at randomisation or history of coagulopathy (y/n) (a hypothesised increased intervention effect in patients with acute coagulopathy/history of coagulopathy at randomisation)
4. History of liver disease (y/n) (a hypothesised increased intervention effect in patients with history of liver disease at randomisation)

5. Type of ICU admission (medical/surgical) (a hypothesised increased intervention effect in surgical patients)
6. Simplified acute physiology score (SAPS) II > 53 points (y/n) (a hypothesised increased intervention effect in the patients with higher SAPS II at randomisation)

Registered variables

Baseline variables

- Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure < 90 mmHg, mean arterial blood pressure < 70 mmHg or lactate > 4 mmol/l)
- Acute or chronic intermittent or continuous renal replacement therapy
- Invasive mechanically ventilation which is expected to last > 24 hours.
- Coagulopathy (platelets < 50 x 10^9/l or international normalized ratio (INR) > 1.5 or prothrombin time (PT) > 20 seconds) documented within the last 24 hours
- Ongoing treatment with anticoagulant drugs (prophylactic doses excluded)
- History of coagulopathy (platelets < 50 x 10^9/l or INR > 1.5 or PT > 20 seconds within 6 months prior to hospital admission
- History of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history)
- Sex
- Age at randomisation/date of birth
- Date of admission to hospital and date and time of admission to ICU
- Elective or emergency surgery during current hospitalization (y/n)
- Treatment of suspected or confirmed *Clostridium difficile* infection during current hospital admission (y/n)
- Treatment with nonsteroidal anti-inflammatory drugs (NSAID) or acetylsalicylic acid at hospital admission (y/n)
- Treatment with anticoagulants at hospital admission (prophylaxis not included) (y/n)
- Intravenous thrombolysis within the previous 3 days (y/n)
- Co-morbidities (defined in appendix 1):
    - history of chronic lung disease
    - history of myocardial ischemia
    - history of severe chronic heart failure (NYHA 3-4)
    - history of chronic renal failure in the last year prior to hospital admission

    - treatment with at least 0.3 mg/kg/day of prednisolone equivalent for at least one month in the 6 month prior to ICU admission
    - active hematologic cancer:
    - metastatic carcinoma
    - acquired immune deficiency syndrome (AIDS)
- Values for SAPS II and severity organ failure assessment (SOFA) scoring 24 hours prior to randomisation.

Daily during ICU admission

- Delivery of trial medication (y/n)
- Open label treatment with PPI/histamine-2-receptor antagonists (y/n)
- Invasive or non-invasive mechanical ventilation (y/n)
- Circulatory support (infusion of vasopressor/inotropes) (y/n)
- Any form of renal replacement therapy (y/n)
- Onset of pneumonia on this day (y/n)
- Treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, or enteral fidaxomicin) for suspected or proven *Clostridium difficile* infection on this day (y/n)
- Acute myocardial ischemia on this day (y/n)
- Enteral feeding on this day (y/n)
- Number of units of red blood cells transfused
- Overt GI bleeding episodes (hematemesis, coffee ground emesis, melena, haematochezia or bloody nasogastric aspirate) (y/n)
- Serious adverse reactions (SARs) (y/n) (appendix 2)

Bleeding form (only for patients with overt bleeding)

- Data on clinically important GI bleeding:
    - A spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
    - start of vasopressor or a 20% increase in vasopressor dose
    - decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
    - transfusion of 2 units of packed red blood cells or more
- Origin of GI bleeding confirmed (y/n)
- Verification of ulcer/gastritis/esophageal varices (y/n)
- Haemostasis achieved/attempted by endoscopy/open surgery/coiling (y/n)

Follow-up 90 days and 1 year after randomisation

- Death (y/n, if yes, date of death)

Missing data

If more than 5% of the observations are missing for any specific analysis that analysis will be conducted both as complete-case and using multiple-imputation based on chained equations. All variables in the specific analysis will be included in the multiple imputation as well as stratification variables (site and presence of haematological cancer), age, SOFA score at baseline, type of admission (medical, elective surgery or emergency surgery), SAPS II at baseline, renal replacement therapy at baseline, mechanical ventilation at baseline, shock at baseline, proportion of patients with clinically important GI bleeding, proportion of patients with one or more episodes of serious adverse events (pneumonia, *Clostridium difficile* infection and myocardial ischemia), and 90-day mortality.

If multiple imputation is used, the primary result of the trial will be based on these data. A 'best-worst, worst-best case' scenario will be used as a sensitivity analysis to assess the potential impact of any pattern of missingness including that the data are missing not at random (MNAR criterion) for the trial results. In the 'best-worst-case' scenario it is assumed that all patients lost to follow-up in the experimental group have had a beneficial outcome (e.g. have survived) and all those with missing outcomes in the control group have had a harmful outcome (e.g. have not survived). Conversely, in the 'worst-best-case' scenario, it is assumed that all patients who were lost to follow up in the experimental group have had a harmful outcome; and that all those lost to follow-up in the control group have had a beneficial outcome.
The unadjusted, non-imputed analysis will also be presented.

General analytic principles

1. All main analyses will compare the two intervention groups in the intention-to-treat (ITT) population.[24–26]
   The ITT population will be all patients randomised except:
   - patients withdrawing consent for the use of data
   - patients who were erroneously randomised AND who did not receive the trial intervention.[27]

   The conclusion of the trial will be based on the ITT analysis
2. In all analyses, a maximum level of 5% (two-sided) type 1 error will be regarded as statistically significant
3. Test-of-interaction will be applied for all subgroup analyses (logistic regression)

Statistical analyses

Trial profile

The flow of trial participants will be displayed in a Consolidated Standards of Reporting Trials (CONSORT) diagram. The number of participants fulfilling the inclusion criteria, the number of excluded participants and reasons for exclusion, and the number of participants included in the final analyses will be presented.

Primary outcome measure

The primary analysis will be a logistic regression analysis adjusted for stratification variables (site and presence of haematological cancer, y/n) of the ITT population. Results will be presented as odds ratios and relative risk ratios (relative risk ratios computed from odds ratios with covariates set to mean values for numeric covariates and the largest group for categorical).

The secondary analysis will be a multiple logistic regression analysis of the ITT population adjusted for stratification variables and additionally differences in potential confounders: age, SOFA score at baseline, and type of admission (medical, elective surgery or emergency surgery). Intervention group and the stratification variable haematological cancer are regarded as fixed effects and trial site is regarded as random effects in the model. Furthermore, frequencies and percentages per group will be reported and an unadjusted Chi-square test for differences in the primary outcome will be provided.

Pre-defined subgroup analyses (see former section) of the ITT population will be conducted using logistic regression analysis adjusted for stratification variables.

A sensitivity analysis of the primary outcome measure including the per-protocol population will be conducted. The per-protocol population will be all randomised patients except those having one or more protocol violations defined as:

- Patients who did not receive the allocated trial intervention at all
- Patients who did not receive the trial intervention for at least two days in a row
- Patients who received treatment (open label) with PPI or histamine-2-receptor antagonists except for those receiving it according to the protocol (i.e. occurrence of GI bleeding after randomisation).
- Patients who withdrew from trial intervention, but consented to the use of data
- Monitoring revealed that one or more in- or exclusion criteria were violated

Secondary outcome measures

The secondary outcomes will only be analysed in the ITT population. The primary analysis of the binary secondary outcome measures will be a logistic regression analysis adjusted for the stratification variables (site and presence of haematological cancer). Results will be presented as odds ratios and relative risk ratios.

Furthermore, frequencies and percentages per group will be reported and an unadjusted Chi-square test for differences in the primary outcome will be provided.

The primary analysis of rate data ('Percentage of days alive without life support in the 90-day period') will be a generalized linear model (initially Poisson distribution, alternatively negative binomial).[28] If the assumptions for Poisson distribution or negative binomial distribution are not met, data will be analysed using the non-parametric Van Elteren test adjusted for site, but no other variables.[29]

The secondary analysis of binary secondary outcomes will be a multiple logistic regression analysis additionally adjusted for differences in potential confounders: age, SOFA score at baseline, and type of admission (medical, elective surgery or emergency surgery).

Interim analysis

The Data Monitoring and Safety Committee (DMSC) will perform two formal interim analyses when 90-day follow-up data of 1650 (approximately 50% of sample size estimation) and 2500 (approximately 75% of sample size estimation) patients have been obtained. For the two intervention groups, the DMSC will evaluate data on:

The primary outcome measure

Mortality 90 days after randomisation of each patient ("landmark mortality").

The secondary outcome measures

- Proportion of patients with one or more of the following adverse events: clinically important GI bleeding, pneumonia, *Clostridium difficile* infection, or acute myocardial ischemia
- Proportion of patients with clinically important GI bleeding
- The occurrence of SARs in the ICU

The DMSC will be provided with the following masked (as group 0 and 1) data from the coordinating centre as:

- Number of patients randomised
- Number of patients randomised per intervention group
- Number of patients stratified per stratification variable per intervention group
- Number of events, according to the outcomes, in the two groups

Based on evaluation of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data. Additionally, the DMSC will yearly be informed about SARs occurring in the two groups of the trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions. The DMSC may recommend pausing or stopping the trial if group-difference in the primary outcome measure, SARs or Suspected Unexpected Serious Adverse Events (SUSARs) are found in the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on O'Brien Fleming alfa-spending function.[30] If an analysis of the interim data from 1650 or 2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the Steering Committee may stop the trial.[26] Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises participant safety. However, stopping for futility to show an intervention effect of 15% RRR or RRI will not occur, as intervention effects less than 15% RRR or RRI in all-cause mortality may be clinically relevant as well.

Ethical approval and Consent to participate

The SUP-ICU trial has been registered on www.clinicaltrials.gov (NCT02467621), the trial is approved by the Danish Health and Medicine Agency (2015030166), the Committees on Health Research Ethics in the Capital Region of Denmark (H-15003141) and by the Danish Data Protection Agency (RH-2015-3203695).

Additionally, the trial is approved by the following ethical committees:

Norway: Regionale Komiteer for Medisinsk og Helsefaglig Forskningsetikk (2015/1490/REK vest)

Finland: Tutkimuseettinen toimikunta (372/2015)

The Netherlands: Medisch Ethische Toetsingscommissie (M15.182376)

Switzerland: Kantonale Ethikkommission Bern (205/15)

Consent will be obtained according to national law. The consenting party will be provided with written and oral information about the trial, so he/she is able to make an informed decision about participation in the trial. Written information and the consent form will be subjected to review and approval by the ethical committee system according to national law in all participating countries. The consenting party can at any time, without further explanation, withdraw consent.

Data sharing statement

The final dataset used for analysis will be shared through an open access data repository

LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
CONSORT	Consolidated Standards of Reporting Trials
CTU	Copenhagen Trial Unit
DASAIM	Danish Society of Anaesthesiology and Intensive Care Medicine
DMSC	Data Monitoring and Safety Committee
GI	Gastrointestinal
ICU	Intensive care unit
INR	International normalized ratio
ITT	Intention-to-treat
NSAID	Nonsteroidal anti-inflammatory drugs
PPI	Proton pump inhibitor
PT	Prothrombin time
RRI	Relative risk increase
RRR	Relative risk reduction
SAPS	Simplified acute physiology score
SAR	Serious adverse reaction
SOFA	Severity organ failure assessment
SSAI	Scandinavian Society of Anaesthesia and Intensive Care Medicine
SUP	Stress ulcer prophylaxis
SUSAR	Severe unexpected serious adverse reaction

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