



## **Stress ulcer prophylaxis in the intensive care unit A multicentre 7-day inception cohort study**

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### **STATEMENT OF COMPLIANCE**

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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**PROTOCOL SYNOPSIS**

<b>Title</b>	Stress ulcer prophylaxis in the intensive care unit. A multicentre 7-day inception cohort study
<b>Objectives</b>	To present data on the prevalence and severity of GI bleeding in critically ill patients in the ICU, and to describe current practice of SUP
<b>Study Design</b>	A multicentre 7-day inception cohort study
<b>Outcomes</b>	Mortality and GI bleeding
<b>Study Duration</b>	7 days
<b>Number of subjects</b>	1,000
<b>Population</b>	Adult critically ill patients in the ICU

**GLOSSARY OF ABBREVIATIONS**

<b>ABBREVIATION</b>	<b>TERM</b>
CRF	Case report form
GI	Gastrointestinal
H2RA	Histamine 2 receptor antagonist
ICU	Intensive care unit
OR	Odds ratio
PPI	Proton pump inhibitor
PI	Principal investigator
SUP	Stress ulcer prophylaxis

## 1. INVESTIGATORS AND FACILITIES

### 1.1 Study Locations

#### Denmark

Department of Intensive Care 4131  
Copenhagen University Hospital Rigshospitalet

Department of Intensive Care Medicine  
Copenhagen University Hospital Bispebjerg

Department of Intensive Care Medicine  
Odense University Hospital

More to be added.

#### United Kingdom

Department of Adult Critical Care  
University Hospital of Wales

More to be added

#### Sweden

To be announced.

#### Norway

To be announced.

#### Iceland

To be announced.

#### Finland

Department of Intensive Care Medicine  
Kuopio University Hospital

More to be added

#### The Netherlands

Department of Critical Care  
University Medical Centre Groningen

#### Italy

San Martino Hospital, Genoa

#### Canada

McMaster University

New Zealand

Department of Critical Care Medicine  
Auckland City Hospital

More to be added.

Australia

To be announced

**1.2 Study Management**

The Steering and Management Committee will manage and coordinate the study centrally. A locale research team consisting of a Principal Investigator and a study coordinator will manage and coordinate the study locally. The Principal Investigator has the responsibility for data collection and maintenance of study documentation (Appendix 1).

**1.2.1 Principal Investigators**Denmark

Mette Krag, MD  
Dept. of Intensive Care 4131  
Copenhagen University Hospital Rigshospitalet

More to be added

United Kingdom

Matthew Wise, MD PhD  
Dept. of Adult Critical Care  
University Hospital of Wales

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John Radcliffe Hospital  
Oxford University Hospitals NHS Trust

More to be added.

Sweden

To be announced.

Norway

To be announced.

Iceland

To be announced.

Finland

Stepani Bendel, MD PhD  
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The Netherlands

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The Netherlands

Italy

Paolo Pelosi  
San Martino Hospital, Genoa

Canada

Deborah Cook, Professor

Australia/ New Zealand

Colin McArthur, MD, Clinical Director  
Department of Critical Care Medicine  
Auckland City Hospital

**1.2.2 Statistician**

To be announced.

**1.2.3 Steering and Management Committee**

Mette Krag, MD  
Dept. of Intensive Care 4131  
Copenhagen University Hospital Rigshospitalet

Morten Hylander Møller, MD PhD  
Dept. of Intensive Care 4131  
Copenhagen University Hospital Rigshospitalet

Anders Perner, MD PhD  
Dept. of Intensive Care 4131  
Copenhagen University Hospital Rigshospitalet

Jørn Wetterslev, MD PhD  
Copenhagen Trial Unit  
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Matthew Wise, MD PhD  
Dept. of Adult Critical Care  
University Hospital of Wales

Colin McArthur, MD, Clinical Director  
Dept. of Critical Care Medicine  
Auckland City Hospital

Stepani Bendel, MD PhD  
Dept. of Intensive Care Medicine  
Kuopio University Hospital

### 1.3 Sponsors

Morten Hylander Møller, MD PhD; Anders Perner, MD PhD  
Dept. of Intensive Care 4131  
Copenhagen University Hospital Rigshospitalet

### 1.4 Funding and resources

The Scandinavian Society of Anaesthesia and Intensive Care Medicine  
Aase and Ejnar Danielsens Foundation

The study is not industrial sponsored.

## 2. INTRODUCTION AND BACKGROUND

### 2.1 Background Information

Critically ill patients are at risk of stress-related gastrointestinal (GI) bleeding<sup>1</sup>. The reported incidences of GI bleeding in the ICU ranges from 2-15%, however, data derives from research published 15-20 years ago<sup>2,3</sup>. As a result of substantial changes in intensive care practice over the last 10-20 years, the incidence of stress ulceration in critically ill patients may have changed.

The two major risk factors for stress-related GI bleeding are mechanical ventilation  $\geq$  48 hours (odds ratio (OR) 15.6) and coagulopathy (OR 4.3)<sup>2</sup>. GI bleeding due to stress ulceration is associated with increased mortality<sup>3</sup>.

Older trials have suggested that SUP can reduce the frequency of GI bleeding in ICU patients compared to placebo or no prophylaxis<sup>4-6</sup>, and SUP is regarded as a standard of care in ICU as outlined by the Surviving Sepsis Campaign guidelines<sup>7</sup>. However, recent research has questioned the rationale and level of evidence of SUP in ICU patients, because of limited data, methodological flaws in some of the trials, a possible increased incidence of nosocomial pneumonia and clostridium difficile enteritis following use of SUP, and general improvements in intensive care<sup>1,8</sup>.

### 2.2 Research Question

#### Specific research questions

“What is the prevalence of GI bleeding in general ICUs in 2013?”

“What is the current practice of SUP in general ICUs in 2013?”

#### Overall research question of the SUP-ICU research programme

“Is SUP indicated for critically ill patients in the ICU?”

### 2.3 Rationale for Current Study

The reported incidence of GI bleeding in the literature is 15-20 years old and varies considerably<sup>9</sup> for several reasons. Firstly no consensus definition of GI bleeding has been used. Secondly GI bleeding data have been derived from different ICU subpopulations. In addition, intensive care practice has markedly changed over the last 20 years, so old data may not inform us about the current incidence. The present use of SUP in the ICU needs to be described, including the preferred SUP agents used. It is unknown which SUP agent has the optimal balance between benefit and harm, and if SUP in the ICU is indicated at all<sup>10</sup>. This is due to high risk of

bias, increased risk of random error as the required information size for a reasonable intervention effect has not yet been reached, and possible design errors and insufficient data on the effect on mortality<sup>9</sup>. Consequently, updated data on current SUP practice in the ICU, and on the incidence and severity of GI bleeding is warranted.

### 3. STUDY OBJECTIVES

#### 3.1 Primary Objective

To describe the prevalence and severity of GI bleeding in critically ill patients in the ICU, and to describe current practice of SUP.

### 4. STUDY DESIGN

#### 4.1 Type of study

A multicentre 7-day inception cohort study investigating the prevalence of GI bleeding and current use of SUP in critically ill patients in the ICU.

#### 4.2 Study design diagram

See Appendix 2 in page 16.

#### 4.3 Number of subjects

A total of 1,000 critically ill patients in general ICUs are expected to be included.

#### 4.4 Expected duration of study

Seven days with 90 days follow-up.

#### 4.5 Primary and secondary outcome measures

##### Primary

Clinical significant GI bleeding

*(Definition: overt GI bleeding AND  $\geq 1$  of the following features within 24 hours of GI bleeding: 1) spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure of 20 mmHg or more, 2) start of vasopressor or a 20% increase in vasopressor dose 3) decrease in hemoglobin of at least 2 g/dl (1.24 mmol/L), or 4) transfusion of 2 units of packed red blood cells or more)*

##### Secondary

Overt GI bleeding

*(Definition: hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate)*

90-day mortality

*(Definition: death within 90-days of the index date)*

Crude and adjusted relative risks for GI bleeding and 90-day mortality

### 5. RECRUITMENT

#### 5.1 Recruitment



Potential subjects will be identified and recruited in the ICU by the locale Principal Investigator.

## 5.2 Eligibility criteria

### 5.2.1 Inclusion Criteria

All adult (age $\geq$ 18 years) critically ill patients admitted acutely to one of the study ICUs during the 7-day study period.

### 5.2.2 Exclusion Criteria

Age $<$ 18 years

Observed upper GI-bleeding and/or treatment for upper GI-bleeding during current hospital admission

Planned ICU admission (e.g. after elective surgery)

Previously ICU admission during current hospital admission before the 7-day study period

## 5.3 Readmission to an ICU

When patients included in the 7-day study period are discharged from the ICU and, during same hospital admission, are readmitted to an ICU participating in SUP-ICU, the day form registration will be continued.

Patients admitted to an ICU during current hospital admission before the 7-day study period will be excluded during screening procedure

## 5.4 Patients transferred between hospitals

Patients transferred from an ICU participating in SUP-ICU to another ICU participating in SUP-ICU: day form registration will be continued at the receiving hospital and the investigator at the last hospital will complete follow-up

Patients transferred from an ICU participating in SUP-ICU to an ICU not participating in SUP-ICU: day form data will no longer be collected, but follow-up data will be registered at day 90

Patients transferred from an ICU not participating in SUP-ICU to an ICU participating in SUP-ICU: the patient cannot be included in the study

## 5.5 Study closure

When the 7-day study period and the 90-day follow-up period has ended.

## 6. CLINICAL AND LABORATORY ASSESSMENTS - METHODOLOGY

An overview is presented in Figure 2, page 16.

### 6.1 Patient evaluation

#### Baseline patient characteristics

1. Age on day of ICU admission (years)
2. Gender (male/female)
3. SAPS 2 on day of ICU admission (0-163 points)
4. SOFA score on day of ICU admission (0-24 points)

5. Days admitted in hospital (days)
6. Treatment with ulcer prophylactic drugs (PPI, H2RA, antacids or sucralfate) prior to hospital/ICU admission
7. Treatment with NSAID/acetylsalicylic acid or anticoagulant drugs prior to hospital/ICU admission
8. Comorbid conditions (choose one or more)
  - a. History of COPD
  - b. History of heart failure or myocardial infarction
  - c. History of chronic renal failure (need for chronic renal support or S-creatinine > 3.6 g/dL / 300 µmol/L prior to hospital admission)
  - d. History of liver cirrhosis or increased bilirubin
  - e. Immunosuppression (at least 0.3 mg/kg per day of a prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission)
  - f. Surgical intervention (elective or emergency) prior to ICU admission?
  - g. Treatment with prednisolone? (at least 0,3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission)
  - h. Coagulopathy during current hospital admission or at ICU admission? (Platelet count < 50 and/or international normalized ratio (INR) > 1,5)

Daily from ICU admission to end of the 90<sup>th</sup> day of follow-up or discharge from ICU

9. Treatment with continuous vasopressor (Noradrenaline, adrenaline, dobutamine, dopamine, vasopressin, levosimendan or milniron)
10. Treatment with continuous/intermittent renal replacement therapy
11. Intubation and mechanical ventilation (invasive)
12. Lowest platelet count the last 24 hours? (if registered)
13. Highest International Normal Ratio (INR) the last 24 hours? (if registered)
14. Treatment with NSAID and acetylsalicylic acid
15. Treatment with anticoagulant drugs
16. Treatment with intravenous thrombolysis
17. Treatment with ulcer prophylactic drugs (PPI, H2RA, sucralfate, antacids, prostanoids)
18. Volume of tube feeding on this day?
19. Post pyloric/jejunal feeding?
20. Any oral intake?
21. Upper GI-bleeding (hematemesis, coffee ground mesis, melena, hematochezia or bloody nasogastric aspirate or positive aspirate blood test without overt bleedig)
22. Clinical significant bleeding (see definition in section 4.5)
23. Endoscopic finding (ulcer, gastritis, esophageal varices)
24. Treatment of bleeding
25. Lowest haemoglobin on the day the patient had upper GI-bleeding
26. Units of red blood cells given on the day the patient had upper GI-bleeding

Day 90 after the study index date

27. Vital status (dead/alive)?
28. Discharged from ICU? (y/n)
29. Length of hospital/ICU admission

## 6.2 Unit/department evaluation

30. Type of Hospital (University/Teaching/District/General/Specialist)?

31. Type of ICU (Medical/Surgical/Mixed)?
32. Number of ICU beds open for admission (e.g. 20)?
33. Does your ICU have a general guideline/protocol for use of SUP? (y/n)
34. Does your ICU have a guideline/protocol for use of SUP in specific subgroup of patients? (y/n)
35. When do you stop SUP? (full enteral feed/discontinuation of mechanical ventilation/ICU discharge/other)
36. Do you consider SUP treatment safe? (y/n)
37. Which (if any) of the following potential adverse effects are you worried about? (Nosocomial Pneumonia/Clostridium difficile enteritis/Abscess formation/Rash/Interstitial Nephritis/Delirium/Cardiac Arrhythmias/Myocardial infarction/Drug Interactions/Death/Other/None)

## 7. STATISTICAL METHODS

### 7.1 Sample size estimation

In a cross sectional study with simple random sampling,  $\alpha=0.05$ ,  $\beta=0.2$ , and an estimated incidence of GI bleeding in the ICU of 2-4%, inclusion of at least 1,000 patients are required<sup>11</sup> to yield a confidence interval of an incidence rate of 2% ranging from 1.1% to 2.9% or for 4% ranging from 2.8% to 5.2%. An estimated 75 ICUs will be needed.

### 7.2 Population to be analysed

All patients who are acutely admitted to one of the study ICUs at any point of the 7-day study period (Monday 00:01 to Sunday 23:59).

### 7.3 Statistical analysis plan

Continuous variables will be evaluated for significant deviations from the normality assumption using the Kolmogorov-Smirnov test and histograms. Non-parametric tests of comparison will be used for variables evaluated as not normally distributed. Difference testing between groups will be performed using analysis of variance, Kruskal-Wallis test, Cochran-Armitage trend test, *t* test, Mann-Whitney test, Chi<sup>2</sup>-test, and Fishers exact test, as appropriate. For multiple comparisons Bonferroni corrected P.values will be presented and evaluated as well. Multivariate logistic regression analysis will be used to determine crude and adjusted risk for GI bleeding and 90-day mortality. Data will be presented as mean (95% confidence interval), median (interquartile range [IQR]), or number (%) as appropriate. All statistical tests will be 2-tailed, and  $P<.05$  is considered statistically significant.

Prior to conducting analysis, a detailed statistical plan will be prepared and made available online ([www.sup-icu.com](http://www.sup-icu.com)).

## 8. DATA HANDLING

### 8.1 Records to be kept / Data Collection

Data will continuously be collected on case report forms (CRFs) from source data (patient records, laboratory reports and surveys) the day the study is conducted. Subsequently, the data on the CRFs is entered into an electronic database.

### 8.2 Data Management / Quality control

The locale Principal Investigators will check the completed CRFs for completeness and accuracy against the source data. Original CRFs will be used when entering information into the electronic database. The database will be checked against the CRFs for accuracy. No investigation of the data will begin until an accurate database has been assured.

### **8.3 Study Record Retention**

All research data and study related documents will be stored confidentially and securely for 15 years in the Department of Intensive Care 4131, Copenhagen University Hospital Rigshospitalet following the end of the study. The members of the Steering and Management Committee have access to the stored data. Upon request, investigators will get data from their own unit.

## **9. ADMINISTRATIVE ASPECTS**

### **9.1 Confidentiality**

Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Subject Identification Number (SIA) to maintain subject confidentiality.

### **9.2 Approvals**

This protocol and any subsequent modifications will be reviewed and approved by the National Data Protection Agencies. A letter of protocol approval by the National Data Protection Agency will be obtained prior to the commencement of the study.

### **9.3 Modifications of the protocol**

The study will be conducted in compliance with the current version of the protocol. Any change to the protocol document that affects the scientific intent, study design, or results is considered an amendment, and therefore will be written and filed as an amendment to the protocol.

### **9.4 Financial Disclosure and obligations**

All participating researchers are obliged to declare any conflicts of interest or financial interest related to the study.

## **10. USE OF DATA AND PUBLICATIONS POLICY**

The study will be reported to the National Data Protection Agencies and Ethics Committee, as appropriate. The final protocol will be available upon request. Upon study completion the main manuscript will be submitted to one of the major clinical

journals regardless of the result, and the results will in any case be published at the SUP-ICU home page ([www.sup-icu.com](http://www.sup-icu.com)). The listing of authors will be as follows: M Krag will be the first author. M Wise / A Perner / M Borthwick / J Wetterslev will be the second, third, fourth and fifth author. MH Møller will be the last and corresponding author, and then 'the SUP-ICU research group and Scandinavian Critical Care Trials Group' will be written. If new members of the Steering and Management Committee are appointed these will also become co-authors if they fulfil the Vancouver definitions. If other trial groups participate these will appear after the SCCTG. The members of the SUP-ICU research group and other persons who contribute considerably will be investigators; these will appear in an appendix to the main paper.

The Steering and Management Committee will grant more personal authorships depending on personal input according to the Vancouver definitions.

Funding sources will have no influence on data handling or analyses or writing of the manuscript.

Publication of data from a single-centre needs to be approved by the Steering and Management Committee. An investigator, a group of investigators or a trial group involved in SUP-ICU can get access to the full dataset to analyze a specific research question. In that case, a written protocol has to be submitted and approved by the Steering and Management Committee.

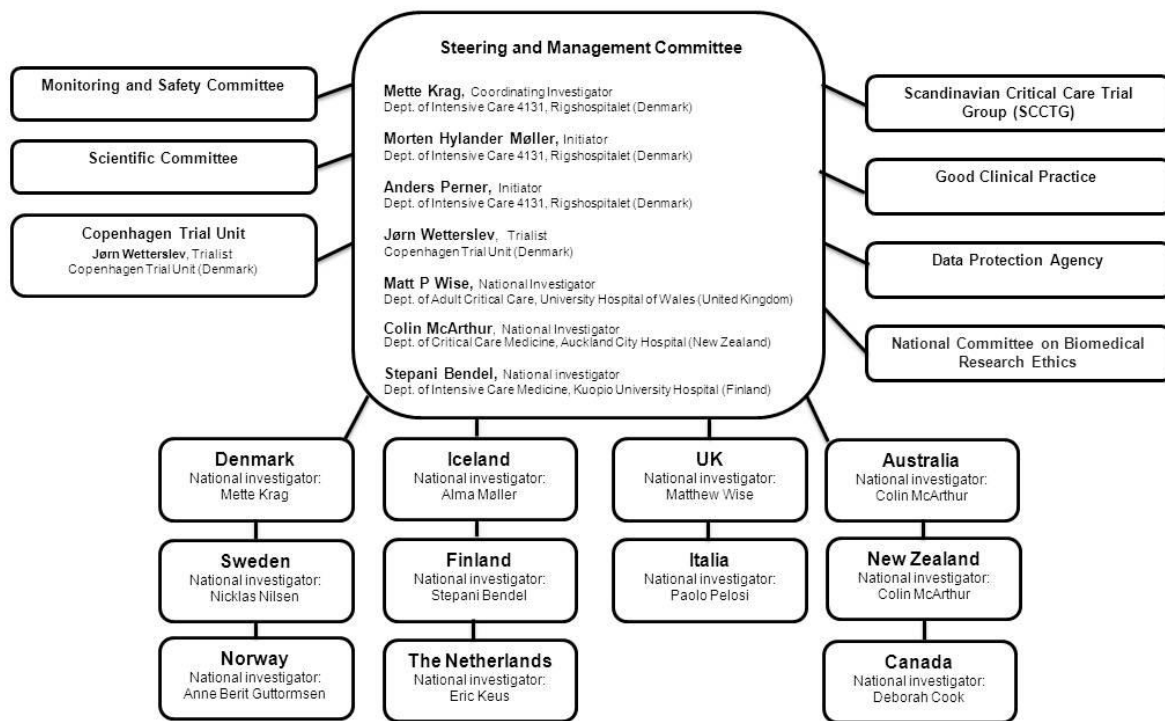
The Steering and Management Committee holds the primary responsibility for publication of the results of the study.

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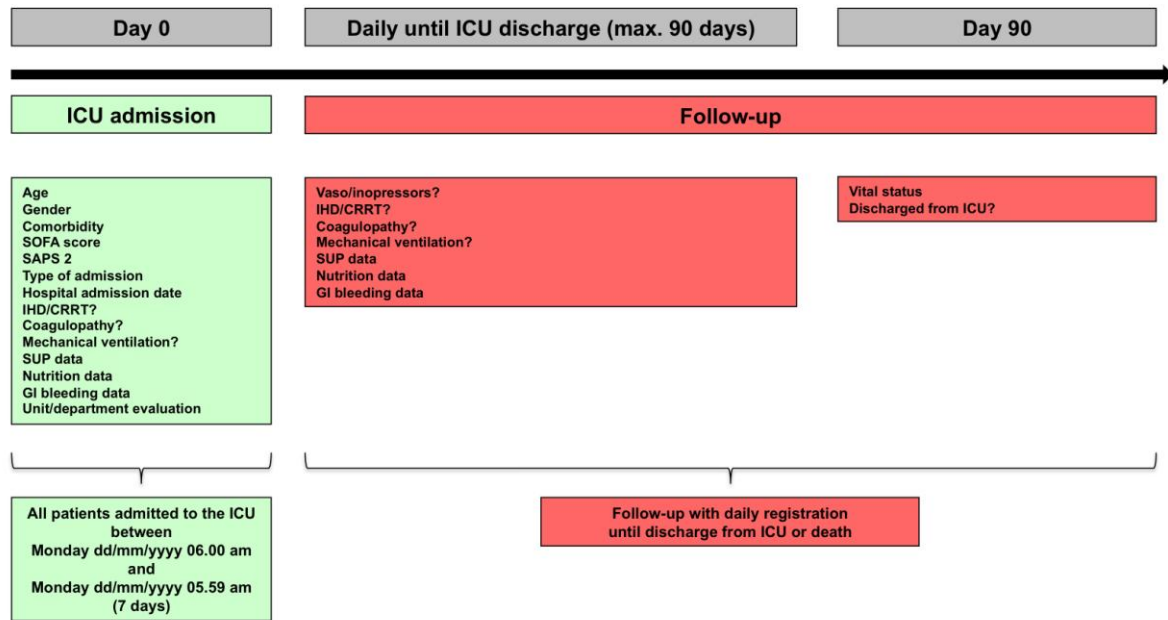
12. APPENDIX 1:

RESEARCH PROGRAMME ORGANISATION



### 13. APPENDIX 2

## STUDY DESIGN DIAGRAM



SUP-ICU study diagram