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Interactions in clinical trials

Protocol and statistical analysis plan for an explorative study of four randomized ICU trials on use of pantoprazole, oxygenation targets, haloperidol and intravenous fluids

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Interactions in clinical trials: Protocol and statistical analysis plan for an explorative study of four randomised ICU trials on use of pantoprazole, oxygenation targets, haloperidol and intravenous fluids

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Abstract

Background: ICU patients receive numerous interventions, but knowledge about potential interactions between these interventions is limited. Co-enrolment in randomised clinical trials represents a unique opportunity to investigate any such interactions. We aim to assess interactions in four randomised clinical trials with overlap in inclusion periods and patient populations.

Methods: This protocol and statistical analysis plan describes a secondary explorative analysis of interactions in four international ICU trials on pantoprazole, oxygenations targets, haloperidol, and intravenous fluids, respectively. The primary outcome will be 90-day all-cause mortality. The secondary outcome will be days alive and out of hospital in 90 days after randomisation. All patients included in the intention-to-treat populations of the four trials will be included. Four co-primary analyses will be conducted, one with each of the included trials as reference using a logistic regression model adjusted for the reference trial's stratification variables and for the co-interventions with interactions terms. The primary analytical measure of interest will be the analyses' tests of interaction. A p-value below 0.05 will be considered statically significant. The stratification variable- and co-intervention-adjusted effect estimates will be reported with 95% confidence intervals without adjustments for multiplicity.

Conclusion: This exploratory analysis will investigate the presence of any interactions between pantoprazole, oxygenation targets, haloperidol, and amount of intravenous fluids in four international ICU trials using co-enrolment. Assessment of possible interactions represents valuable information to guide the design, statistical powering, and conduct of future trials.

Keywords: Intensive Care Units; Critical Illness; Randomised Controlled Trials; Pragmatic Clinical Trials; Drug Interactions; Pantoprazole; Oxygen Inhalation Therapy; Haloperidol; Infusions, Intravenous

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1. Introduction

When accepting co-enrolment in randomised clinical trials, assessment of possible interaction between interventions is important¹⁰⁻¹², both to establish the possible impact of co-enrolment on the results of each trial, and to identify inconspicuous interactions. Intensive care unit (ICU) patients receive numerous interventions, but the knowledge about any potential interaction between these interventions is limited. Co-enrolment in randomised clinical trials represents a unique option to investigate such interactions. The Centre for Research in Intensive Care (CRIC) has initiated four randomised clinical trials in adult ICU patients. All interventions tested were considered standard of care in everyday clinical practice in ICUs. All trials were generally conducted in the same sites, had overlapping inclusion criteria and inclusion periods, and co-enrolment was allowed. The trials were the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial investigating pantoprazole versus placebo in patients at risk of gastrointestinal bleeding;^{1,3} the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial investigating a lower versus a higher oxygenation target in patients with acute hypoxaemic respiratory failure;^{4,9} the Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU) trial investigating haloperidol versus placebo in patients with delirium;⁶ and the Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care (CLASSIC) trial investigating restrictive versus standard intravenous fluid therapy in patients with septic shock.⁵ This explorative study aims to investigate potential interaction between the four interventions in these four international randomised clinical trials. We hypothesise that no significant interactions exist. Here we describe the rationale, methods, and detailed statistical analysis plan of the study.

2. Methods

2.1. Study design

This is a protocol and detailed statistical analysis plan for an explorative analysis of interactions of interventions in the SUP-ICU,^{1,3} HOT-ICU,^{4,9} AID-ICU,⁶ and CLASSIC⁵ trials. The four trials were all investigator-initiated, pragmatic, international, randomised, parallel-group trials in adult ICU patients. The SUP-ICU and AID-ICU trials were placebo-controlled with blinding of patients, clinicians, outcome assessors, and trial statisticians, whereas the HOT-ICU and CLASSIC trials were open-label with blinded statistical analyses. This manuscript has been finalised prior to extraction of any data on co-enrolled patients in the four trials. The protocol adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (STROBE checklist is presented in Appendix S1).¹³

2.2. Approvals and registrations

All trials were approved by the Danish Medicines Agency (SUP-ICU: RH-ITA-006, 2015030166, EudraCT no. 2015-000318-24; HOT-ICU: AAUH-ICU-01, 2017021858, EudraCT no. 2017-000632-34; AID-ICU: 2017101527, EudraCT no. 2017-003829-15; CLASSIC: RH-ITA-007, 2018020596, EudraCT no. 2018-000404-42), the relevant Danish regional committees on health research ethics (SUP-ICU: H-16036585, HOT-ICU: N-20170015, AID-ICU: SJ-646, CLASSIC: H-18006255), the Danish Data Protection Agency (SUP-ICU: RH-2015-3203695, HOT-ICU: 2008-58-0028, AID-ICU: REG-169-2017, CLASSIC: VD-2018-39), and by all required authorities in participating countries. All trials were prospectively registered at www.ClinicalTrials.gov (SUP-ICU: NCT02467621, HOT-ICU: NCT03174002, AID-ICU: NCT03392376, CLASSIC: NCT03668236). All patients in the four trials were enrolled after consent to participate had been obtained according to national regulations.

2.3. Setting

Participants in the four trials were recruited in 64 ICUs in university and non-university hospitals in Denmark, Belgium, the Czech Republic, Finland, Iceland, Italy, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom. Not all sites participated in all four trials. There were various degrees of overlap in inclusion periods, with only the HOT-ICU trial overlapping all other trials. The SUP-ICU trial was the first trial to be initiated in January 2016 and completed inclusion in October 2017; the results have been published.^{3,14} The HOT-ICU trial was initiated in June 2017 and finished inclusion in August 2020; the results have been published.⁹ Inclusion into the AID-ICU and CLASSIC trials was initiated in June 2018 and November 2018, respectively, and is currently ongoing. Fig. 1 presents an overview of the inclusion periods and trial overlap.

Fig. 1

2.4. Participants and data

We will include all patients from the intention-to-treat populations of the four trials in our study.¹⁵ The expected cumulated number of included participants is 8,832, not accounting for co-enrolments. The inclusion and exclusion

criteria for each trial vary.^{1,4-6} However, common for all trials is that they included patients aged 18 years or above who were in an ICU or were planned to be admitted to one (the latter applied only for the CLASSIC trial).

Co-enrolment was registered in the electronic case report forms (eCRFs). Patients who were co-enrolled will be identified by their unique national identification number (Denmark)¹⁶ or by comparison of semi-individual data and specific inquiries (other countries).

All relevant data is registered in the respective trials' eCRFs, which are all supplied and supported by the Copenhagen Trial Unit using the clinical data management system OpenClinica® software (OpenClinica, LLC, Waltham, MA 02451, USA).

2.5. Individual trial designs, interventions and results

2.5.1. SUP-ICU

The SUP-ICU trial investigated intravenous pantoprazole 40 mg versus matching placebo once daily from randomisation until ICU discharge or death, for up to 90 days including ICU readmissions. The trial included 3,298 adult patients (≥ 18 years of age) acutely admitted to the ICU with at least one of the following risk factors for gastrointestinal bleeding: shock, use of anticoagulant agents, renal replacement therapy, mechanical ventilation (expected to last > 24 hours), any history of liver disease, or any history of ongoing coagulopathy.^{1,2} No statistically significant between-group difference in the primary outcome being 90-day all-cause mortality was found.³

2.5.2. HOT-ICU

The HOT-ICU trial investigated a targeted arterial oxygen tension (PaO_2) of 8 kPa (lower-oxygenation target) versus a targeted PaO_2 of 12 kPa (higher-oxygenation target) from randomisation until ICU discharge or death, for up to 90 days including ICU readmissions. The trial included 2,928 adult patients with hypoxaemic respiratory failure acutely admitted to the ICU, who were receiving at least 10 litres of oxygen in an open system or who had an FiO_2 of at least 0.50 in a closed system, had an arterial line in place, and were expected to receive supplemental oxygen for at least 24 hours in the ICU.^{4,7} No significant between-group difference in the primary outcome being 90-day all-cause mortality was found.⁹

2.5.3. AID-ICU

The AID-ICU trial investigates intravenous haloperidol 2.5 mg three times daily during ICU delirium plus up to five additional daily similar doses if needed, versus matching placebo from randomisation until ICU discharge or death, for up to 90 days including ICU readmissions. The trial includes adult patients in the ICU with delirium diagnosed using a validated screening tool being either the Confusion Assessment Method – Intensive Care Unit (CAM-ICU)¹⁷ or the Intensive Care Delirium Screening Checklist (ICDSC).¹⁸ The primary outcome is days alive and out of hospital in the 90 days following randomisation.^{6,8} Inclusion to the trial is ongoing, by September 6, 2021 a total of 864 out of 1000 planned participants have been included.

2.5.4. CLASSIC

The CLASSIC trial investigates restrictive versus standard intravenous fluid therapy from randomisation to ICU discharge or death, for up to 90 days including ICU readmissions. The trial includes adult patients acutely admitted to the ICU, or planned to be so, with septic shock according to the Sepsis-3 criteria,¹⁹ i.e. suspected or confirmed site of infection or positive blood culture, ongoing vasopressor or inotrope agent, a lactate of ≥ 2 mmol/L, and who have received at least 1 litre of intravenous fluid in 24 hours prior to randomisation. The primary outcome is 90-day all-cause mortality.⁵ Inclusion to the trial is ongoing, by September 10, 2021 a total of 1456 out of 1554 planned participants have been included.

2.6. Outcome measures

In this explorative study, the primary outcome measure will be 90-day all-cause mortality from the time of randomisation in the reference trial. The secondary outcome measure will be the cumulated number of days alive and out of hospital within the 90-day period from the time of randomisation in the reference trial. This secondary outcome measure will not be evaluated with the SUP-ICU trial as reference, as data on this outcome were not collected in this trial.

2.7. Statistical analysis plan

2.7.1. General analytical principles

All analyses will be conducted according to the intention-to-treat principle including all patients randomised, except those excluded post-randomisation due to in-eligibility before the trial intervention was given in the placebo-blinded trials (SUP-ICU and AID-ICU), and participants where follow-up data could not be obtained due to withdrawal of consent according to national regulations.¹⁵

For all analyses, a p-value below 0.05 will be considered statistically significant. No adjustments for multiplicity will be conducted, as all analyses are considered explorative only.

2.7.2. Study profile

Inclusion, exclusion, and co-enrolment of patients in the four trials will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement²⁰ in a modified CONSORT diagram as presented in Fig. 2.

Fig. 2

2.7.3. Missing data

If less than 5% of data are missing for variables included in any analysis, a complete case analysis will be performed without imputation. If more than 5% of data are missing for a given variable in one of the trials, multiple imputation will be performed using chained equations to create at least 10 imputed data sets in each treatment group.^{21,22} For any multiple imputation conducted, we will use all reference trial stratification variables together with reference trial outcomes and baseline characteristics, as specified in the detailed statistical data analysis plans for each trial.^{2,5,7,8} If multiple imputation is used, all outcome analyses will be based on the imputed data.

2.7.4. Primary outcome

The primary analytic outcomes of interest will be the results of the tests for interactions of the overlapping interventions as follows: (a) pantoprazole versus placebo and higher versus lower oxygenation targets, (b) higher versus lower oxygenation targets and haloperidol versus placebo, (c) higher versus lower oxygenation targets and intravenous fluid restriction versus standard care, and (d) haloperidol versus placebo and intravenous fluid restriction versus standard care. We will conduct four co-primary analyses on the primary outcome, one with each trial as reference, using generalised linear models with logit-links and binomial error distributions (logistic regression) adjusted for the respective reference trial stratification variables as well as for the interventions in the co-enrolled trials with interaction terms. Effects estimates of the interactions will be readily available as odds ratios (ORs) in the regression models and will be reported with 95% confidence intervals (CIs). In the adjustment for the stratification variable *site*, the sites with fewest randomisations will be pooled as necessary to obtain convergence in the models. All patients randomised in the reference trial will be included in each analysis according to the intention-to-treat principle as specified. For each non-reference intervention assessed for interaction, patients will be divided into three groups 'intervention', 'control' or 'not participating'. All patients with 90 days or less between randomisations will be considered co-enrolled, regardless of the chronological order of the randomisations, i.e. regardless of whether the patient was included in the reference or the non-reference trial first. Patients included into two trials, with more than 90 days between randomisations, however, will be marked as 'not participating' in the non-reference trial.

Given the study design, for each combination of interventions, two tests for interaction will be performed, one with each of the trials as reference. If statistical significance in the tests for interaction between the two interventions differs depending on the reference trial, the interaction will be considered of less significance.

For all four trials, to establish the possible impact of co-enrolment on the primary trial conclusions, we will report ORs of the primary outcomes with 95% CIs adjusted for reference trial stratification variables and for the co-enrolled non-reference interventions. The corresponding p-values will be reported as well. If significant interactions between any of the four interventions are identified, the analyses will be conducted as interaction-adjusted for these interventions. For non-significant interactions we will adjust for the co-enrolled interventions without accounting for interactions. In any case, the analyses adjusted for stratification variables and for co-enrolled interventions without adjustment for interactions will be reported as well.

Effect estimates and p-values from the tests of interactions with interventions in co-enrolling trials for each of the reference trials will be presented together with the stratification-variable- and co-enrolment-adjusted effect estimates and p-values of each reference trial in four separate tables. All analyses of interactions will be supplemented with margin plots to illustrate possible interactions.

2.7.5. Secondary outcome

The secondary analyses of days alive and out of hospital in the 90-day period will be conducted using a general linear model for the mean adjusted for the respective reference trial stratification variables as well as for the interventions in the

co-enrolled trials with interaction terms. To enable interaction assessments, the general linear model will be applied regardless of expected non-parametric data distributions for this outcome. The interaction coefficients will be readily available from the analyses and will be reported with 95% confidence intervals (CIs). All analyses will be supplemented with margins plots of the interactions. The stratification variable and co-intervention adjusted effect estimates of the interventions of the reference trial will be reported with 95% CI and corresponding p-values. If significant interactions between any of the four interventions are identified, the analyses will be conducted as interaction-adjusted for these interventions. For non-significant interactions we will adjust for the co-enrolled interventions without accounting for interactions. The analyses adjusted for stratification variables and for co-enrolled interventions without adjustment for interactions will be reported, regardless of whether any significant interactions are identified.

2.7.6. Baseline Parameters

Common baseline parameters in the four trials will be reported for all patients, and for patients co-enrolled in two or more trials, respectively, as numbers and percentages for categorical variables, and medians with interquartile ranges (IQRs) or means \pm standard deviations for continuous variables, as appropriate. For co-enrolled patients the baseline parameters reported, will be those from the time of randomisation into the first trial. Time between randomisations will be reported as well.

3. Dissemination

Study results will be sought published in a relevant peer reviewed journal regardless of whether they can be considered positive, neutral, or negative.

4. Discussion

Co-enrolment within independent randomised clinical trials represents a unique opportunity to investigate potential interactions between the investigated interventions and may identify clinically relevant causal interactions between seemingly unrelated interventions. Such interactions are difficult to identify outside the setting of randomised trials. The current protocol publication with statistical analysis plan represents a detailed overview of the methods and statistical analyses, which will be employed to evaluate interactions between the use of pantoprazole, oxygenation targets, haloperidol, and intravenous fluids in four independent randomised clinical trials conducted in ICU patients.

4.1. Strengths

This protocol and analysis plan has been completed prior to randomisation of the last patient in two of the four trials and before any data for the study have been extracted from the respective trial databases. It adheres to current recommendations and guidelines.¹³ The study profits of the high methodological standards of four large scale international pragmatic randomised clinical ICU trials,^{1,3-6,9} on which it is based, ensuring a high external validity of the findings.

4.2. Limitations

The four trials were not powered to evaluate interactions between the interventions, which would require larger sample sizes.¹² Along this line, the proportions of co-enrolled patients may be small. Furthermore, the evaluation of four separate interactions without adjustments for multiplicity increases the risks of spurious findings, especially since a clear pathophysiological explanation between possible interactions may not be obvious. Therefore, all results can only be considered exploratory and should solely not inform clinical practice. Nevertheless, results may be hypothesis-generating for future studies and will aid in the design of future trials.

In conclusion, the outlined exploratory analysis of four randomised clinical trials will provide important data on interactions between use of pantoprazole, oxygenation targets, haloperidol, and intravenous fluids in the ICU.

Additionally, it will evaluate the possible impact of co-enrolment on the primary conclusions of the four clinical trials.

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Authors' contribution

OLS wrote the first draft of this protocol, which was critically revised by all authors. All authors are all involved in the management and conduct of at least one of the four randomised clinical trials.

Figure legends

Fig. 1 Inclusion periods in the four trials. *Expected number of included patients (ongoing trials). SUP-ICU: the Stress Ulcer Prophylaxis in the Intensive Care Unit trial; HOT-ICU: the Handling Oxygenation Targets in the Intensive Care Unit trial; AID-ICU: the Agents Intervening against Delirium in the Intensive Care Unit trial; CLASSIC: the Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care trial.

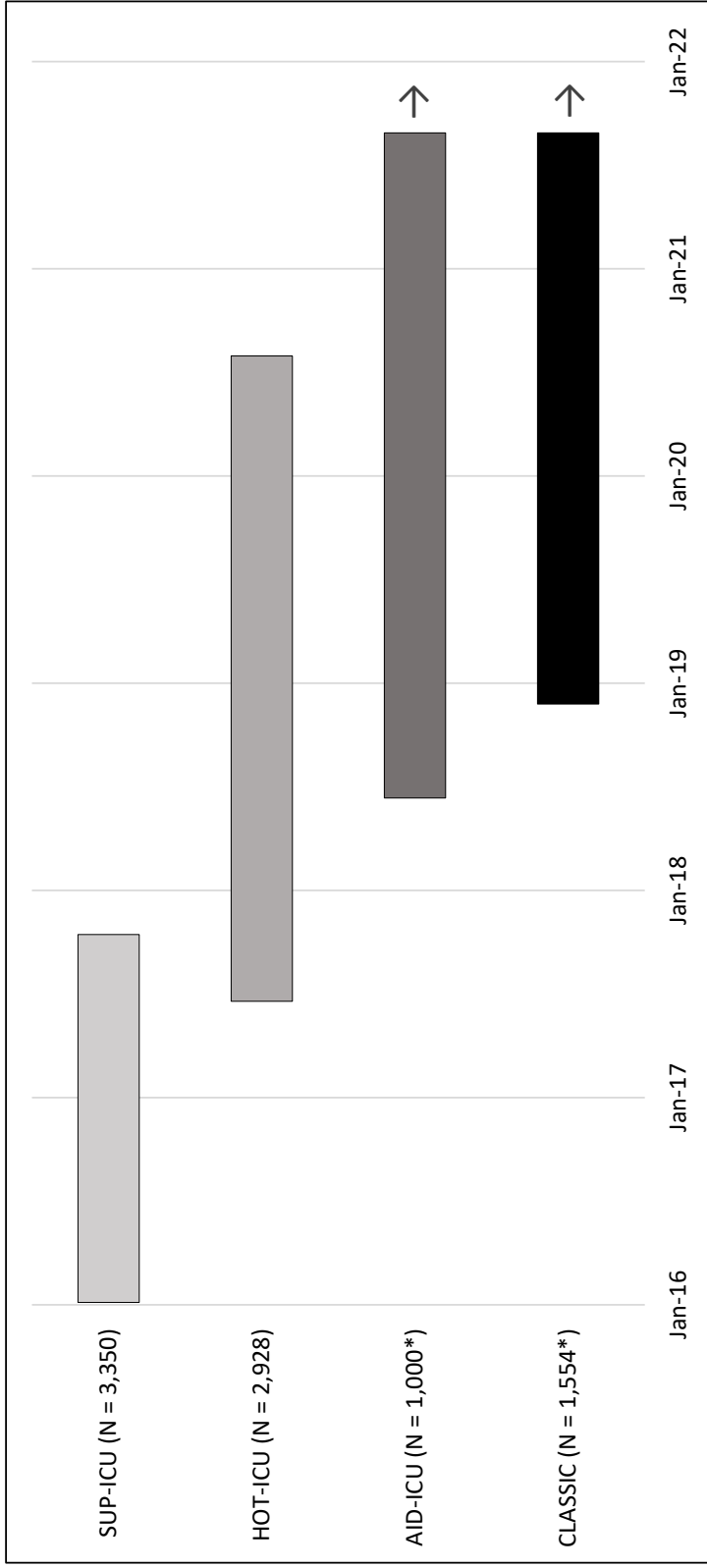
Fig. 2 Modified Consolidated Standards of Reporting Trials (CONSORT) diagram. SUP-ICU: the Stress Ulcer Prophylaxis in the Intensive Care Unit trial, HOT-ICU: the Handling Oxygenation Targets in the Intensive Care Unit trial, AID-ICU: the Agents Intervening against Delirium in the Intensive Care Unit trial, CLASSIC: the Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care trial, PaO₂: arterial oxygen tension. ^a'Restrictive' and 'Standard' denominate the intravenous fluid strategies in the CLASSIC trial. ^bNumber of patients in the analysis of the primary outcome of 90-day all-cause mortality, patients allocated to treatments, but not analysed, are excluded due to negative or unobtainable consent or lost to follow-up.

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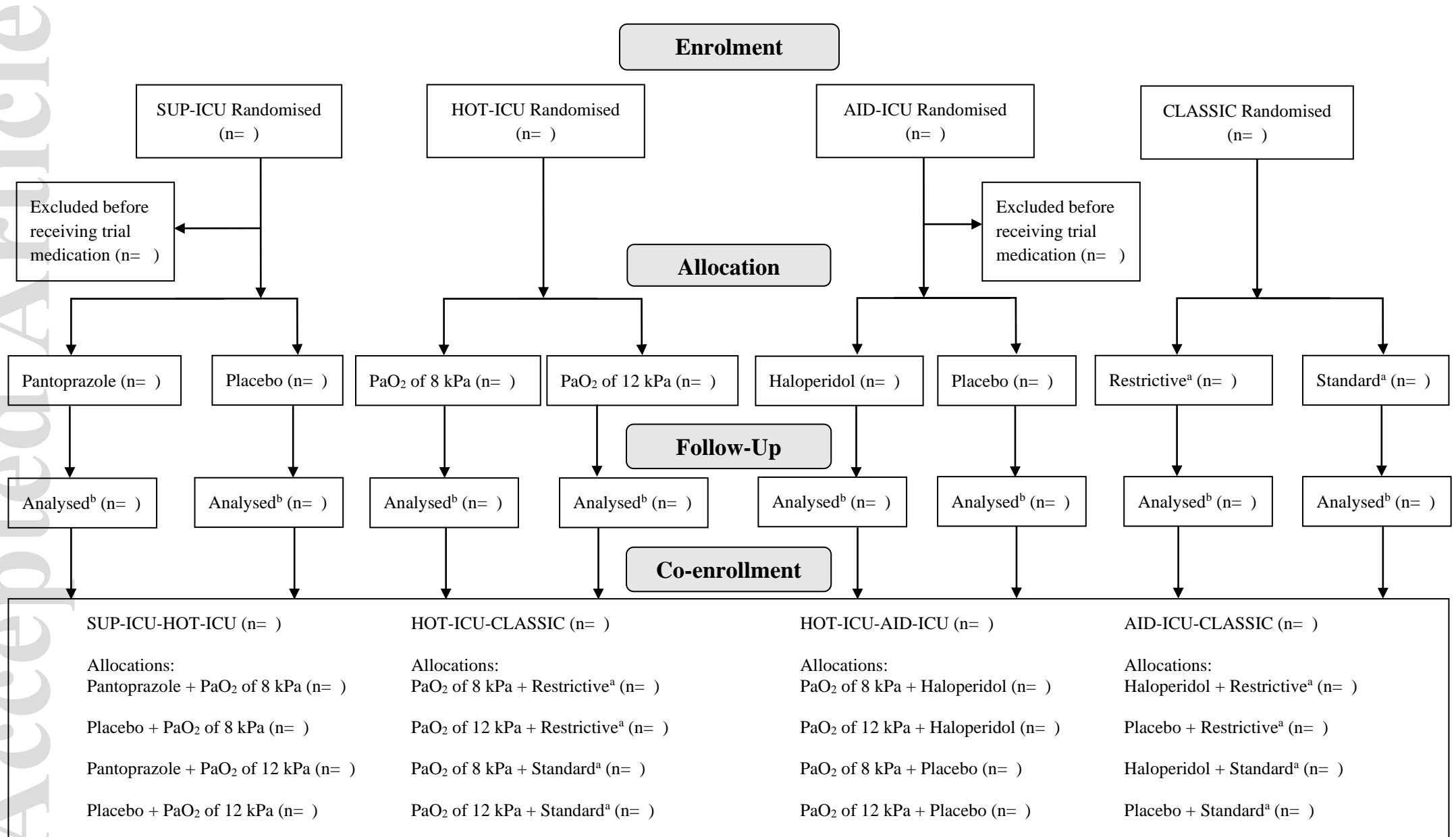


Fig. 2 Modified Consolidated Standards of Reporting Trials (CONSORT) diagram

SUP-ICU: Stress Ulcer Prophylaxis in the Intensive Care Unit trial, HOT-ICU: Handling Oxygenation Targets in the Intensive Care Unit trial, AID-ICU: Agents Intervening against Delirium in the Intensive Care Unit trial, CLASSIC: Conservative versus Liberal Approach to fluid therapy of Septic Shock in Intensive Care trial, PaO₂: arterial oxygen tension. ^a'Restrictive' and 'Standard' denominate the intravenous fluid strategies in the CLASSIC trial. ^bNumber of patients in the analyses of the primary outcome of 90-day mortality, patients allocated to treatments, but not analysed, are excluded due to negative or unobtainable consent or lost to follow-up.