CHECKLIST-ICU Trial

Checklist during multidisciplinary daily visits and clinician prompting for reduction of mortality in intensive care units: a cluster randomized trial

Coordinators and Sponsors:
Research Institute at Hospital do Coração (IEP-HCor)
Instituto D’Or de Pesquisa e Ensino (IDOR)
Hospital Samaritano São Paulo
Hospital Moinhos de Vento

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Study Record Detail:
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CORRESPONDENCE

Research Institute at Hospital do Coração (IEP-HCor)
Rua Abílio Soares, nº 250 – Paraíso
CEP: 04005-000 São Paulo, SP – Brazil
Phone: +55 11 3053 -6611 Extension: 8102
Fax: +55 (11) 3886-4695

Principal Investigator:
Alexandre Biasi Cavalcanti
E-mail: abiasi@hcor.com.br

Research Coordinators:
Karina Normilio da Silva
E-mail: knsilva@hcor.com.br
Viviane Caetano Chiattone
E-mail: vchiattone@hcor.com.br

Instituto D’Or de Pesquisa e Ensino (IDOR)
Rua Diniz Cordeiro, n° 30 – Botafogo
CEP: 22281-100, Rio de Janeiro, RJ – Brazil
Phone: +55 (21) 2538-3541

Principal Investigators:
Fernando Bozza
E-mail: bozza.fernando@gmail.com
Jorge Salluh
E-mail: jorgesalluh@gmail.com

Hospital Samaritano São Paulo
Rua Conselheiro Brotero, 1513 – Consolação
CEP: 01232-010 – São Paulo, SP – Brazil
Phone: +55 (11) 3821-5391
Fax: +55 (11) 3821-5821

Principal Investigator:
Valquiria Pelisser
E-mail: valpelisser@terra.com.br

Research Coordinator:
Patrícia Vendramim
E-mail: patriciavendramim@samaritano.org.br

Hospital Moinhos de Vento
Rua Ramiro Barcelos, 910 – Moinhos de Vento
CEP: 90035-001 Porto Alegre – RS
Phone: +55 (51) 3314-3434

Principal Investigator:
Cassiano Teixeira
E-mail: cassiano.rush@gmail.com
Description of intensive care units (ICUs) based on the Resolution of the Collegiate Board of Directors (RDC) no. 7/2010 and RDC no. 26/2012
Assessment of the frequency of use to measures to prevent complications in ICU and clinical outcomes
Assessment of safety culture applying the Safety Attitudes Questionnaire
Data collection in 152 ICUs:
- Individual data of 60 consecutive eligible patients/ICU

Concealed randomization
\( N \geq 102 \) ICU

Phase II – Intervention

**Intervention Group**
Checklist during multidisciplinary daily visits + clinician prompting
Data collection:
- Individual data from 60 consecutive patients
- Applying of Safety Attitudes Questionnaire

**Control Group**
Usual care including multidisciplinary daily visit
Data collection:
- Individual data from 60 consecutive patients
- Applying of Safety Attitudes Questionnaire

Primary Outcome: In-hospital mortality, truncated at 60 days

Study completion

**Intervention Group**
After completion of Phase II, the intervention group should keep the use of the checklist during multidisciplinary daily visits + clinician prompting
There will not be data collection for research purposes.

**Control Group**
After completion of Phase II, the control group will be trained to start using the checklist during multidisciplinary daily visits + clinician prompting
There will not be data collection for research purposes.
SYNOPSIS

<table>
<thead>
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<th>Title</th>
<th>CHECKLIST-ICU Trial</th>
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<table>
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<th>Study Design</th>
<th>Cluster randomized trial in intensive care units (ICUs) in Brazil and Latin American countries. The study will be conducted in two phases:</th>
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<tr>
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<td>o Patients’ characteristics: baseline data from 60 consecutive patients in each participating ICU. Assessment of the frequency of use to measures to prevent complications in ICU and clinical outcomes.</td>
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<tr>
<td></td>
<td>o Assessment of safety culture: Applying of Safety Attitudes Questionnaire (Adapted from the SAQ);</td>
</tr>
<tr>
<td></td>
<td>• Phase II – Intervention:</td>
</tr>
<tr>
<td></td>
<td>o It is the main phase for data analysis. After randomization, the ICUs randomized to the experimental group receive the interventions. Data collection from 60 consecutive patients per ICU. Assessment of adherence to measures to prevent complications in ICU and clinical outcomes.</td>
</tr>
<tr>
<td></td>
<td>o Assessment of safety culture: Applying of Safety Attitudes Questionnaire (Adapted from the SAQ).</td>
</tr>
</tbody>
</table>

| Bias Control | Concealed randomization. Intention-to-treat analysis |

| Primary Objectives | 1) To check whether the use of intervention, including 1) checklists containing daily care goals during the multidisciplinary visit, and 2) clinician prompting, can reduce in-hospital mortality of patients admitted to intensive care units. |
|                   | 2) To characterize the participating ICUs according to the criteria of the following ANIVISA resolutions: RDC no. 7/2010 and RDC no. 26/2012. |

| Eligibility | Inclusion criteria for the cluster:                                                                                           |
|            | • Intensive care units (ICUs), except for exclusively cardiac ICUs and semi-intensive care units.                             |
|            | • ICUs that are willing to implement or have already implemented multidisciplinary visits with at least a physician and a nurse at least on all working days. |
|            | Exclusion criteria for the cluster:                                                                                         |
|            | • ICUs that already use multiple-item checklist during multidisciplinary visit.                                              |
|            | Inclusion criteria for patients:                                                                                           |
|            | • Adult patients (≥ 18 years) with length of ICU stay longer than 48 hours.                                                   |
|            | Exclusion criteria for patients:                                                                                           |
|            | • Moribund patients, with high probability of death between the 48th and 72th hour of ICU stay.                              |
|            | • Patients admitted to the ICU only for palliative care.                                                                   |
|            | • Patients with a diagnostic hypothesis or confirmed diagnosis of brain death.                                               |
| **Intervention Group** | Intervention associated with daily visit (at least a physician and a nurse on weekdays) applied to all patients from ICU admission to discharge. The intervention will include:  
- Checklist with:  
  - Multiple items for prevention of ICU complications and use of evidence-based interventions.  
  - Definition of daily care goals during multidisciplinary visits.  
- Clinician prompting: Nurse (or resident physician) reviews checklist and prompts ICU physician if any adjustments are needed. |
| **Control Group** | Usual care including daily visit (at least a physician and a nurse on weekdays). |
| **Follow-up** | Until hospital discharge (Maximum: 60 days of ICU admission) |
| **Outcomes** | **Primary:**  
  - In-hospital mortality, truncated at 60 days  
 **Secondary:**  
  - Secondary outcomes of adherence to appropriate care processes:  
    - Head of bed elevated at 30° in eligible patients;  
    - Adequate prevention of venous thromboembolism;  
    - Rate of use of central line catheter;  
    - Rate of use of indwelling urinary catheter;  
    - Patient-days under appropriate sedation, i.e., arousal in response to verbal stimulation or alert and calm (RASS -3 to 0) in patients on mechanical ventilation;  
    - Tidal volume ≤ 8mL/kg in patients on mechanical ventilation;  
    - Patients-day receiving enteral or parenteral feeding;  
  - Secondary outcome of safety culture:  
    - Score on the "Safety Attitudes Questionnaire"  
  - Secondary outcomes of clinical results:  
    - ICU mortality;  
    - Mechanical ventilation-free days at 28 days;  
    - Central line-associated bloodstream infection (CLABSI) rate;  
    - Rate of ventilator-associated pneumonia (VAP);  
    - Urinary tract infection (UTI) rate;  
    - Length of ICU stay;  
    - Length of hospital stay. |
| **Duration of Phases** | Phase I: one year.  
Phase II: one year |
| **Sample size** | Phase II will include at least 102 intensive care units and 60 patients per unit. With 102 ICUs and average of at least 50 patients per unit, the study will have a power of 90% and 
a type I error of 5% to detect an absolute reduction in in-hospital mortality of 6% (from 30% in the control group to 24% in the experimental group), considering a coefficient of variation (K) of 0.25, and appropriate analysis adjusted for cluster effect.  
The sample size may be adjusted after analyzing the in-hospital mortality rate and the coefficient of variation (K) in the database (phase I). |
| **Statistical Analysis** | The analysis will follow the principle of intention-to-treat. As the randomized units will be the hospitals, but the outcomes will be assessed at the patient’s level, the analysis will consider the cluster effect. Thus, the primary outcome, in-hospital mortality, will be analyzed with random effects logistic regression, |
considering a fixed effect intercept for the strata and adjusting for ICUs’ standardized mortality ratio (calculated with SAPS 3) observed in the observational phase and patients’ SAPS 3 score observed in the randomized phase.
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List of Abbreviations

AMIB – Brazilian Association of Intensive Care Medicine (Associação de Medicina Intensiva Brasileira)
CPGDC – Clinical Practice Guideline Development Cycle
REC - Research Ethics Committee
GEE – Generalized estimating equations
CLABSI – Central line-associated bloodstream infection
UTI – Urinary tract infection
VAP – Ventilator-associated pneumonia
SAPS3 – Simplified Acute Physiology Score
ARDS – Acute respiratory distress syndrome
SAQ – Safety Attitudes Questionnaire
NICD – Nosocomial infection control department
SOFA – Sequential Organ Failure Assessment
IUC – Indwelling urinary catheter
ICF – Informed consent form
VTE – Venous thromboembolism
DVT – Deep vein thrombosis
ICU – Intensive care unit
MV – Mechanical ventilation
Introduction

In-hospital mortality rate of adult patients admitted to intensive care units (ICUs) is high in Brazil. According to the EPIMED® database, which includes 87 ICUs of public hospitals and 350 ICUs of private hospitals in Brazil, the in-hospital mortality rate of ICU patients is 21%. However, when considering only public ICUs this rate is 36% (EPIMED 2012 – unpublished data). There is no accurate data on the total number of adult ICU patients in Brazil. However, it is possible to estimate the number of ICU admissions in Brazil considering a rate of 32 admissions per ICU bed per year (EPIMED 2012 – unpublished data) and an availability of 20,731 ICU beds for adults (AMIB census data). This results in an estimate of approximately 663,000 ICU admissions per year in Brazil, and considering the in-hospital mortality rate of ICU patients of 21% (EPIMED 2012 – unpublished data), 139,312 deaths.

Checklists can be useful to prevent medical errors, increase the likelihood of the use of evidence-based interventions and improve clinical outcomes of patients. Checklists have been widely used in aviation and manufacturing industry to avoid omissions while performing complex procedures. More recently, successful cases have been reported with the use of checklists in healthcare. It is possible to mention notable examples, such as the use of the checklist of the World Health Organization (WHO) for Safe Surgery\(^1\) and the checklist of the Keystone ICU Project to prevent central line-associated bloodstream infection\(^2\).

The checklist of the WHO for Safe Surgery contains 19 items that are checked orally by the surgical team before induction of anesthesia (sign in), before skin incision (time out) and before the patient leaves the surgical unit (sign out)\(^3\). The effectiveness of the checklist was tested in before-and-after study conducted in four hospitals in developed countries (Australia, the United States, England, and New Zealand) and four hospitals in developing countries (Philippines, India, Jordan, and Tanzania). There was a reduction in mortality and major complications after implementation of the checklist (Table 1).
Table 1. Main results of the study Safe Surgery Saves Lives Study Group

<table>
<thead>
<tr>
<th>Centers</th>
<th>Deaths</th>
<th>Any complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Low income</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>High income</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>1.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

The Keystone ICU Project involved the implementation of some actions in 108 ICUs in Michigan, USA. The use of a simple eight-item checklist by nurses during central line catheter insertion and the instruction that the nurse should request the interruption of the procedure if any of the items were not complied with, except in emergency situations, were some of the actions implemented. The use of this checklist resulted in a 66% reduction in the rate of central line-associated bloodstream infection, and half of the participating ICUs achieved zero rate of bloodstream infection.

Use of checklists during ICU daily visit

The FAST HUG checklist is a mnemonic for "Feeding", "Analgesia", "Sedation", "Thrombosis prophylaxis", "Head of bed elevated", "Stress Ulcer prophylaxis," and "Glucose control". It was proposed by Jean-Louis Vincent as a simple tool to be used in daily visits and became very popular.

Studies evaluating the effect of checklists on ICU daily visits have demonstrated their usefulness in identifying omission errors and good acceptance by the medical team. A study conducted in a trauma ICU has shown that the checklist reduces clinical complications, such as ventilator-associated pneumonia (VAP), and that such effect is maintained over a one-year period. In particular, the mandatory verbal review of the checklist by the multidisciplinary team during the visit increased the attention to various items, such as deep vein thrombosis prophylaxis, stress ulcer prophylaxis, or oral care for patients on mechanical ventilation.

It is possible that a substantial part of the effect of the checklists on clinical outcomes is mediated by cultural changes and teamwork improvement, rather than being the product of direct action in the target items (e.g.: deep vein thrombosis prophylaxis or elevated head of bed). Factors such as improved communication among health care team members, reduced
hierarchical distance between the intensivist and the other health care professionals, and nurses' perception that they are active and important participants in this process can help to improve the quality of care.\(^7,8\)

All studies using checklists in ICUs have are before-and-after studies, i.e., with substantial risk of bias. A systematic review on the use of checklists in acute care environments (ICU, walk-in clinic, surgical center) identified nine studies, five of which were conducted in ICUs, all of them including historical controls.\(^9\) In most studies, but not in all of them, there was improvement in patient safety. However, because of the risk of bias due to the study design, evidence level was low. Therefore, the authors concluded that studies of higher methodological quality are needed to assess the effectiveness of the checklists.

**Assessment of Daily Care Goals**

Effective communication among the members of the multidisciplinary team is essential for high-quality care of critically ill patients. Multiple tasks need to be performed so that the ICU patient can recover and be discharged. Some of the tasks are: request and evaluation of tests, establishment of correct diagnoses, prevention of complications, prescription of appropriate treatments, removal of invasive devices, sedation and administration of vasoactive drugs whenever appropriate, pain control, delirium and anxiety discharge planning, among others.

Multidisciplinary daily visits are essential so that the team is able to discuss the case and clearly establish each patient's needs. However, there are often failures in establishing clear daily care goals for each patient. A study conducted in an ICU at the Johns Hopkins Hospital found that less than 10% of residents and nurses understood which were the daily care goals for the patients.\(^10\) To solve this problem, the intensivists implemented a checklist including the explicit establishment of the daily care goals. The checklist was completed during the daily visit and signed by the intensivist. After that, all members of the multidisciplinary team wrote their initials in the checklist three times a day (morning, afternoon, and evening shifts). After implementing the checklist containing the daily care goals, 95% of residents and nurses started to understand the daily care goals. Concomitantly, the authors observed a significant reduction in mean length of ICU stay from 2.2 to 1.1 days.

**Clinician Prompting**

The method used to implement the checklists can make a difference in the results. In a study conducted in a clinical ICU in the United States, the resident physician informed the intensivist
(clinician prompting) whenever any of the checklist items had been omitted from the discussion during the multidisciplinary daily visit. In this study, another ICU located in the same hospital was used as control. This ICU simultaneously implemented the checklist in the daily visits, but without using the clinician prompting strategy.

Compared with the control ICU, the ICU that used clinician prompting had an increase in the number of mechanical ventilation-free days, reduction in the time of use of empiric antibiotics and central line catheter, and an increase in the number of prescriptions of deep venous thrombosis and stress ulcer prophylaxis. The ICU mortality adjusted for risk was also reduced (odds ratio 0.36; 95%CI 0.13 to 0.96). The results are impressive, but should be interpreted with caution due to non-random allocation of the intervention and the fact that the analysis does not consider the cluster effect, which was even more impressive because there were only two clusters.

**Objectives**

**Primary Objective**

The primary objectives are:

1. To check whether the use of intervention, including 1) checklists containing daily care goals during the multidisciplinary visit, and 2) clinician prompting, can reduce in-hospital mortality of patients admitted to intensive care units.
2. To describe the participating ICUs according to the criteria of the RDC no. 7/2010 and RDC no. 26/2012.

**Secondary Objectives**

1. To check the effect of a multifaceted intervention on the following outcomes:
   a. Outcomes of processes:
      - Head of bed elevated at 30° in patients eligible;
      - Adequate prevention of venous thromboembolism;
      - Rate of use of central line catheter;
      - Rate of use of indwelling urinary catheter;
      - Patient-days under mild sedation or alert and calm (RASS -3 to 0) in patients on mechanical ventilation;
      - Tidal volume ≤ 8mL/kg in patients on mechanical ventilation;
- Patients-day receiving enteral or parenteral feeding;

b. Quality culture:
   - Score on the domains of the adapted Safety Attitudes Questionnaire;

c. Clinical outcomes:
   - ICU mortality;
   - Mechanical ventilation-free days at 28 days;
   - Central line-associated bloodstream infection (CLABSI) rate;
   - Rate of ventilator-associated pneumonia (VAP);
   - Urinary tract infection (UTI) rate;
   - Length of ICU stay;

2. In the event of reduction in in-hospital mortality associated with the study intervention, to determine which were the mediators of effect, improvement in the indicators of the processes targeted in the items of the checklist and/or improvement in the safety culture of the ICUs.

**Study Design**

Cluster randomized trial in intensive care units (ICUs) in Brazil.

The study will be conducted in two phases as follows:

**Phase I – Baseline data**

In this phase, data will be collected to characterize the ICUs, care processes, and clinical outcomes.

At the beginning of Phase I, the adapted Safety Attitudes Questionnaire (SAQ) will be administered to the staff members of the participating ICUs.

The ICUs will be described according to the criteria proposed in the RDC no. 7/2010 and RDC no. 26/2012. Nine-two variables related to a substantial and representative sample of the recommendations of the RDC no. 7/2010 and RDC no. 26/2012 will be collected.

The description of care processes and clinical outcomes involves the collection of data from 60 patients, which includes the collection of data on admission and follow-up data until hospital discharge (limited to 60 days of hospital stay). Each ICU shall complete this phase within at most 6 months after ethical approval.
With the purpose of solving possible asynchrony for the beginning of data collection and variation in the number of admissions among the ICUs, a one-year deadline was set out for completion of this phase. Only those ICUs that effectively collect individual data of 60 consecutive patients in an adequate manner within six months during Phase I will participate in Phase II.

Phase II – Intervention

It is the main phase for data analysis. The ICUs will be randomly allocated to intervention or control group. The ICUs randomized to the experimental group will receive the study interventions.

The units of randomization (ICUs) will not be allowed to move from the control group to the intervention group or vice versa. However, the ICUs will be analyzed in the group where they were allocated to (intention-to-treat analysis).

Individual data collection of 60 consecutive patients per ICU will be carried out. Each ICU shall complete this phase within at most 6 months after ethical approval. Again, because the dates of training and beginning of the intervention phase may not be simultaneous among the units, the total duration of this phase shall be one year.

At the end of Phase II, the adapted Safety Attitudes Questionnaire (SAQ) will be administered again to the staff member of the participating ICUs, including both the ICUs of the intervention group and those of the control group.

**Randomization**

The unit of randomization is the ICU. In hospitals with more than one ICU, the ICUs will be considered separate units of randomization provided that the care teams are different. If the health care teams are the same in the various ICUs of a single hospital, all ICUs will be considered a single cluster.

The list of stratified and block randomization will be generated using appropriate statistical package. Stratification will be performed according to the median of in-hospital mortality found in phase I.
The allocation of the intervention (experimental group or control group) will be performed by the statistician of the IEP-HCor, who will receive only the identification code of the unit, but will not be aware of the identity of the ICU. Thus, we will ensure allocation blinding.

The statistician will inform the research manager about the allocation for each unit identification code. The research manager of the IEP-HCor will then inform the ICUs about the group they were allocated to.

**Participants**

**Participating ICUs**

Inclusion criteria for the cluster:

- Intensive care units, except for exclusively cardiac ICUs and semi-intensive care units;
- ICUs that are willing to implement or have already implemented multidisciplinary visits with at least a physician and a nurse at least on all working days.

Exclusion criteria for the cluster:

- ICUs that already use multiple-item checklist during multidisciplinary visit. We defined that there is systematic use of the checklist when all the following criteria are present:
  - Content: structured assessment (according to printed or digital document) of multiple items focused on the prevention of usual ICU complications (e.g.: VAP, DVT, and CLABS) and/or explicit definition of daily goals;
  - Time: checklist use for more than 30 days (as observed in assessment visit to the ICU during Phase I);
  - Frequency: at least three days a week;
  - Method: verbal, observational (another professional does the checking), with or without a written record.

**Participating patients**

Inclusion criteria for patients:

- Adult patients (≥ 18 years) with length of ICU stay longer than 48 hours.

Exclusion criteria for patients:
• Moribund patients, with high probability of death between the 48th and 72nd hour of ICU stay.
• Patients admitted to the ICU only for palliative care.
• Patients with a diagnostic hypothesis or confirmed diagnosis of brain death.

Interventions

Intervention to improve the quality of care in intensive care units. The intervention will include:

• Checklist to be used during daily multidisciplinary visits;
• Clinician prompting: Nurse or resident physician reviews checklist and prompts ICU physician if any adjustments are needed.

Checklist

The purpose of the checklist is to avoid omission errors while providing evidence-based care to critically ill patients and to make the communication of daily care goals clear for the entire multidisciplinary team. The checklist should be reviewed aloud during the daily multidisciplinary visit and signed by the on-duty intensivist (or the on-call physician if there is not an on-duty physician) and nurse.

Development of Checklist

The checklist should include:

• Multiple items related to the prevention of ICU complications and evidence-based treatments (e.g.: adequate prophylaxis for venous thromboembolism and low tidal volume for patients with Acute Respiratory Distress Syndrome (ARDS));
• Definition of the daily care goals of the daily visit.

A preliminary version of the checklist is shown in Appendix A. The final version will be prepared following the steps 1-5 shown below, adapted from the Clinical Practice Guideline Development Cycle - CPGDC, a transparent process for the development of evidence-based guidelines.12

Step 1: Initially the members of the Steering Committee will list some items that should potentially be included in the checklist. The items to be considered are:
1. VTE prophylaxis;
2. Screening for severe sepsis;
3. Adjust/discontinue antibiotics;
4. Remove central line catheter;
5. Remove indwelling urinary catheter;
6. Head of bed elevated at 30° or more;
7. Pain;
8. Sedation;
9. Discontinuation of MV;
10. Maximal tidal volume
11. Use of chlorhexidine 2x daily;
12. Diet adjustment;

**Step 2:** Next, we will perform an extensive search in the medical literature to identify evidence on interventions in critical care medicine reporting clinically relevant outcomes. We will look for systematic reviews of randomized clinical trials. When no recent systematic reviews about the topic are found (<5 years), we will prepare a review.

**Step 3:** Based on the systematic reviews, we will use the GRADE system to classify the level of evidence and strength of recommendation.\(^{13, 14}\) In addition to the quality of evidence and strength of recommendation, the Steering Committee listed several criteria, arranged in a questionnaire, to assess which items should be included in the checklist. The questionnaire (Table 2) will be completed for each item under consideration for the checklist. During this phase, the Steering Committee will develop a pilot version of the checklist.

**Step 4:** Iterative testing of the checklist will be performed to obtain a pre-final version. The objectives will be to evaluate the language (if the items are clear, objective, and brief), the time required to use the checklist, and method of use (e.g.: nurse reads the items)? Check off each item in pen or just check them orally?).

**Step 5:** The final step is to present the evaluation of each item under consideration for the checklist in a formal consensus conference involving the participating ICUs randomized to the intervention group. The purpose of the consensus conference will be to approve the recommendations to be included in the final checklist.
The checklists will be arranged in a notebook. There will be a daily checklist on each page. On the cover of the notebook there will be a table for the record of cultures collected and antibiotics in use.

**Table 2. Criteria to include the item in the checklist:**

<table>
<thead>
<tr>
<th>Checklist item:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is the relevance of the outcome(s) affected by the checklist item?</td>
</tr>
<tr>
<td>( ) Critical [e.g.: death] ( ) Important ( ) Moderate [e.g.: pressure ulcer]</td>
</tr>
<tr>
<td>2. Is the recommendation strong? Consider the determinants of the strength of recommendation:</td>
</tr>
<tr>
<td>a. Level of evidence (GRADE: Risk of bias, inconsistency, inaccuracy, indirect evidence, publication bias)</td>
</tr>
<tr>
<td>( ) High ( ) Moderate ( ) Low ( ) Very Low</td>
</tr>
<tr>
<td>b. Is the balance between desirable and undesirable effects (adverse events and discomfort) favorable?</td>
</tr>
<tr>
<td>( ) Highly favorable ( ) Close balance of advantages and disadvantages</td>
</tr>
<tr>
<td>c. Costs (allocation of resources: training, human resources [complex interventions], financial resources)</td>
</tr>
<tr>
<td>( ) High ( ) Low</td>
</tr>
<tr>
<td>d. Variability (or uncertainty) in the values and preferences</td>
</tr>
<tr>
<td>( ) High ( ) Low</td>
</tr>
<tr>
<td>Based on the above mentioned considerations, the strength of recommendation is:</td>
</tr>
<tr>
<td>( ) Strong ( ) Weak</td>
</tr>
<tr>
<td>3. Applicable to most ICU patients</td>
</tr>
<tr>
<td>( ) All [100%] ( ) Many [30 to &lt;100%] ( ) Few [&lt;30%]</td>
</tr>
<tr>
<td>4. Complication is common, serious and costly?</td>
</tr>
<tr>
<td>( ) Meets three criteria ( ) Two criteria ( ) One or less</td>
</tr>
<tr>
<td>5. Omission is common (at the individual level, e.g.: oral chlorhexidine is a common omission in ICUs, but, in the ICUs using chlorhexidine, omission is rare at the individual)</td>
</tr>
<tr>
<td>( ) Yes ( ) No</td>
</tr>
<tr>
<td>6. You can generate an objective question (recommendation) associated with a clear intervention</td>
</tr>
<tr>
<td>( ) Yes ( ) No</td>
</tr>
</tbody>
</table>
 Clinician Prompting

Every afternoon, the nurse or resident should review the checklists of all patients and take note of any pending items in the "List of Patients with Pending Items" (Appendix A). The items of the List of Patients with Pending Items address six topics:

1) Prevention of DVT/pulmonary embolism;
2) Consider the possibility of removing central line access;
3) Consider the possibility of removing indwelling urinary catheter;
4) Consider stopping or reducing the dose of sedatives;
5) Consider spontaneous breathing trial for patients on mechanical ventilation;
6) Address care goal not met for the day.

Next, the nurse or resident should contact the on-call physician requesting solution of the pending items using pre-defined questions of the Clinician Prompting - Script.1

Strategies for implementing the interventions of the study

Based on successful deployment of checklists in prior settings\(^1,^2,^11\) we were keen to encourage a specific deployment strategy that would help the checklist to be successful. Specifically, we wished to create a flat hierarchy, empowering the entire team to actively participate in rounds. That is, we expected to leverage the checklist potential not only to make sure important care interventions are not forgotten but also to promote a healthy team dynamic in which the team leader (usually the senior attending) listens well to the staff. Our implementation strategy to facilitate the use of the checklists and clinician prompting in the ICUs of the experimental arm are grouped in seven categories detailed in table 3.
Table 3. Strategies for implementing the interventions of the study

**Experimental arm investigators meeting.** The medical director and nursing director of all ICUs randomized to the experimental arm are invited to attend a one-day meeting. The objectives of the meeting are to present the rationale for the study interventions and the results of the observational phase (baseline results of ICU characteristics, adherence to healthcare processes, patient outcomes and safety climate), to vote on the items for the checklist and to provide training on the use of the study interventions.

**Initiation visit of randomized phase.** All sites in the experimental arm are visited by one intensivist from the Steering Committee. In these visits, we present the study design, adherence and clinical results of the observational phase, the checklist and definition of targets for improvement to the multidisciplinary ICU team. We also participate in multidisciplinary rounds to train the teams on the application of the checklist and definition of daily goals.

**Audit & feedback:** We generate monthly reports regarding the rates of adherence of selected processes of care using data collected on the study electronic case report forms. These reports include goals for each process of care so that we can classify the rate of adherence as “achieve the goal,” “close to the goal” or “do not achieve the goal”. Goals are defined based on compliance rates with the care processes obtained in the observational phase. We send these reports and schedule monthly conferences to discuss them with the ICU nursing and physician directors.

**Contacts with ICU medical and nursing directors:** The coordination center contacts the ICU medical and nursing directors if the checklist or clinician prompting is not being used regularly.

**Study website:** A study website is available with articles, study materials, videos and a forum to post questions, share experiences and images such as photos of the rounds.

**Active reminders:** We send SMS messages one to three times a week in the morning to staff from all experimental group ICUs to remind them of the time of the daily visit with the checklist and in the afternoon to remind them about clinician prompting.

**Videos:** Videos are presented in the training visits and are available on the study website, accessible only by health professionals working at the experimental arm ICUs. The videos contain material on how to use the checklist, how not to use the checklist and two video testimonials of well-known opinion leaders (Mr Paul O’Neill and Dr Derek Angus) that focus on successful quality improvement experiences, patient safety, leadership and team communication.
Strategies for recruiting ICUs and patients

All members of the AMIB, the research networks AMIB-Net and BRICNet and those included in the email lists of intensivists will be invited to participate in the trial. In addition, we will ask the regional coordinators of the AMIB to send invitations to their members. Also, we will disclose the study on the AMIB website and in scientific meetings of intensivists.

Recruitment and follow-up of patients should be enabled by: 1) understanding of the participating ICUs that the main objective of the project is to enable substantial advances in the care of severely ill patients; 2) simplicity of the study procedures, limiting the workload for researchers; 3) transfer of the grant to the person responsible for data collection in the centers.

Appendix C shows a list of centers that accepted the initial invitation to join the study.

Outcomes

The definitions of the outcomes, who assesses, when and how the assessment is done are presented in Table 4. The primary outcome and the secondary outcomes of adherence to processes and clinical results are listed below.

Primary

- In-hospital mortality, truncated at 60 days;

As we will consider for analysis only patients with length of ICU stay longer than 48 hours, we will assess only deaths occurring after that period. We chose this approach because deaths occurring within the first 48 hours of ICU admission have little potential to respond to interventions to improve quality of care proposed in the study. Conversely, interventions (checklists and clinician prompting) will be applied daily to all patients, from ICU admission to discharge.

Secondary

Adherence to processes

We will evaluate the following secondary outcomes that demonstrate adherence to appropriate care processes:
- Head of bed elevated at 30° in patients eligible;
- Adequate prevention of venous thromboembolism;
- Rate of use of central line catheter;
- Rate of use of indwelling urinary catheter;
- Patient-days under mild sedation or alert and calm (RASS -3 to 0) in patients on mechanical ventilation;
- Tidal volume ≤ 8mL/kg in patients on mechanical ventilation.
- Patients-day receiving enteral or parenteral feeding;

Secondary outcomes related to adherence to processes will be evaluated by an investigator who does not provide care for ICU patients. We consider the inclusion of a health professional of the nosocomial infection control department.

**Safety Culture**

To assess the safety culture we will use the validated Portuguese version of the Safety Attitudes Questionnaire (SAQ)\(^\text{15, 16}\), which was associated with improvement in indicators that demonstrate patient safety, such as rates of hospital infection\(^\text{17, 18}\). Additionally, these questionnaire has good psychometric properties (Cronbach’s alpha 0.7 to 0.8) and is sensitive to assess individual safety attitudes. We will apply this instrument before and after the study intervention.

**Clinical Results**

We will evaluate the following secondary outcomes that demonstrate clinical results:

- ICU mortality;
- Mechanical ventilation-free days at 28 days;
- Central line-associated bloodstream infection (CLABSI) rate;
- Rate of ventilator-associated pneumonia (VAP);
- Urinary tract infection (UTI) rate;
- Length of ICU stay;
- Length of hospital stay;

**Data Collection**

**Characteristics of ICUs**
The ICUs will be described according to the minimum requirements for the operation of intensive care units proposed in the RDC no. 7/2010 and RDC no. 26/2012. Nine-two variables related to a substantial and representative sample of the recommendations of the RDC no. 7/2010 and RDC no. 26/2012 will be collected. Data collection for the description of the characteristics of the ICU will be performed by health professionals of the coordinating institutions during on-site visit to the participating ICUs.

It is important to highlight that the characteristics of each unit will always be treated confidentially and the data will be reported in an aggregate manner. That is, the results will describe the set of ICUs instead of every individual ICU.

**Characteristics of Patients – individually assessed**

Data will be collected from 60 patients in the phases of baseline data (Phase I) and randomization (Phase II) by a health professional not associated with patient care. We recommend that a staff member of the Nosocomial infection control department (NICD) performs this task.

*Baseline Visit:*

- Date of birth;
- Sex;
- Data for the SAPS3 (Simplified Acute Physiology Score) and SOFA (Sequential Organ Failure Assessment);
- Main category of disorders that prompted the ICU admission;

*Daily ICU visits:*

Data will be collected during the ICU stay for a limited period of 15 days:

- Fully completed checklist;
- Completed clinician prompting form;
- Daily multidisciplinary visit;
- Use of MV;
- Occurrence of VAP;
- Occurrence of CLABSI;
- Occurrence of urinary tract infection;
• Occurrence of Acute Respiratory Distress Syndrome;
• Use of central line catheter;
• Use of indwelling urinary catheter;
• Indicators of the processes listed in Table 3 (e.g.: the head of the bed elevated at 30° or more, VTE prevention, level of sedation).

ICU discharge visit

• Vital status;
• Date of ICU discharge.

If the hospital stay extends beyond 60 days, the discharge visit will be held on the 60th day, and we will consider this date as the date of alive hospital discharge.

Hospital discharge visit:

• Vital status;
• Date of hospital discharge.

As mentioned above, if the hospital stay extends beyond 60 days, the discharge visit will be held on the 60th day, and we will consider this date as the date of alive hospital discharge.

Safety Culture

All physicians, nurses, practical nurses, and physical therapists of the participating ICUs will be invited to complete the Portuguese version of the Safety Attitudes Questionnaire. Other professionals of the ICU interdisciplinary team may also be invited to complete de questionnaire (e.g.: nutritionists, psychologists, speech therapists, pharmacists, occupational therapists, social workers, etc.). With that purpose, we will ask the principal investigators at each center to prepare a list including the names of the professionals in their unit. The professional who will perform data collection in the unit will be responsible for ask the staff members to complete the questionnaires.

The investigators of each ICU will be responsible for publicizing the initiative and asking all critical care physicians, nurses, practical nurses/nursing assistants, and physical therapists to complete the SAQ at the beginning of Phase I and at the end of Phase II of the study.

The goal of the ICUs will be to collect questionnaires from at least 75% of the professionals. This goal must be achieved in Phase I so that the ICU participates in Phase II of the project.
goal must be achieved in Phase II so that the team of researchers from the ICU is mentioned in the project publications.

**Blinding**

It is not feasible to blind researchers, health care teams, and patients to the study intervention. The members of the outcome assessment committee will be blinded.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Who assesses</th>
<th>When to assess</th>
<th>How to assess</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality, truncated at 60 days</td>
<td>$= \frac{\text{in-hospital deaths}}{\text{hospital discharges}}$</td>
<td>Professional who does not provide care for ICU patient</td>
<td>Hospital discharge. Follow-up limited to 60 days after ICU admission.</td>
<td>Consider only patients eligible for the study</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>$= \frac{\text{ICU deaths}}{\text{ICU discharges}}$</td>
<td>Professional who does not provide care for ICU patient</td>
<td>ICU discharge</td>
<td>Consider only patients eligible for the study</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>$= \text{Length of ICU (days)}$</td>
<td>Professional who does not provide care for ICU patient</td>
<td>ICU discharge</td>
<td>Consider only patients eligible for the study</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>$= \text{Length of hospital (days)}$</td>
<td>Professional who does not provide care for ICU patient</td>
<td>Hospital discharge. Follow-up limited to 60 days after ICU admission</td>
<td>Consider only patients eligible for the study</td>
</tr>
<tr>
<td>Mechanical ventilation-free days at 28 days</td>
<td>$= \text{Survival time regardless of invasive mechanical ventilation in the first 28 days after join the study}$ Patients who were discharged alive and regardless of the invasive MV before 28 days are considered to be alive and regardless the MV of hospital discharge until the 28th day.</td>
<td>Professional who does not provide care for ICU patient</td>
<td>28 days after ICU admission</td>
<td>Consider only patients eligible for the study</td>
</tr>
</tbody>
</table>

*We will consider to be cases of hospital discharge those patients who stay in hospital 60 days after ICU admission.
**Table 4. Outcomes (continued)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Who assesses</th>
<th>When to assess</th>
<th>How to assess</th>
</tr>
</thead>
</table>
| **Head of bed elevated at 30°**                                         | \[\text{number of patient} - \text{days with head of bed elevated at } \geq 30° \]
|                                                                        | \[\text{eligible patient} - \text{days}\]                                                         | Professional who does not provide care for ICU patient | Daily in the ICU | Bed observation. Consider only patients with indication of head of the bed at 30° (MV, enteral feeding or altered level of consciousness) |
| **Adequate prevention of venous thromboembolism**                       | \[\text{number of patient} - \text{days with adequate DVT prevention} \]
|                                                                        | \[\text{patient} - \text{days}\]                                                                 | Professional who does not provide care for ICU patient | Daily in the ICU | Check prescription. Consider only patients eligible for the study.          |
|                                                                        | Adequate prevention of VTE will be defined as:                                                   |                                                   |                 |                                                                                |
|                                                                        | • Dalteparin 5.000U 1x a day SC, enoxaparin 40mg 1x a day SC or heparin                          |                                                   |                 |                                                                                |
|                                                                        | 5.000U 12/12hs SC or fondaparinux 2.5 mg SC or 1x. A higher dose can be used if the patient has indication of anticoagulation therapy. |                                                   |                 |                                                                                |
|                                                                        | • If heparin is contraindicated: compression stockings ± pneumatic compression                   |                                                   |                 |                                                                                |
| **Patients-day receiving enteral or parenteral feeding**                | \[\text{number of patient} - \text{days receiving enteral or parenteral diet} \]
|                                                                        | \[\text{patient} - \text{days}\] \times 100                                                     | Professional who does not provide care for ICU patient | Daily in the ICU | Check prescription. Consider only patients eligible for the study.          |
| **Patients under adequate sedation**                                    | \[\text{number of patient} - \text{days under adequate sedation} \]
|                                                                        | \[\text{patient} - \text{days on MV}\]                                                          | Professional who does not provide care for ICU patient | Daily in the ICU | Assess RASS once a day. Consider only patients eligible for the study.       |
Table 4. Outcomes (continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Who assesses</th>
<th>When to assess</th>
<th>How to assess</th>
</tr>
</thead>
</table>
| Tidal volume ≤ 8mL/kg of predicted weight | \[
\text{patient} - \text{days TV} \leq 8\text{mL per Kg predicted weight} \times 1000
\] | Professional who does not provide care for ICU patient | Daily in the ICU | Consider only patients eligible for the study |

Central line-associated bloodstream infection (CLABSI) rate

\[
\text{number of CLABSI} \times 1000
\]

Bloodstream infection defined according to the CDC criteria

Rate of ventilator-associated pneumonia (VAP)

\[
\text{number of PAVs} \times 1000
\]

Rate of urinary tract infection associated with catheter (UTI)

\[
\text{number of UTIs} \times 1000
\]

Rate of mechanical ventilation

\[
\text{number of patient} - \text{days on MV} \times 100
\]

Scores on the six domains of the Safety Attitudes Questionnaire

Score on the six domains of the Safety Attitudes Questionnaire

Self-administration. Principal investigator is responsible for asking the patient to complete the questionnaire.

At the beginning of Phase I and at the end of Phase II

All physicians, nurses, practical nurses, and physical therapists of the ICU Goal: at least 2/3 of health professionals.
Managing and Controlling Data Quality

Electronic Data Collection System

The IEP-HCor Data Management System is a web-based system developed by a team of programmers at IEP-HCor to run on a Microsoft SQL platform®. The system has the following functions: patient registration, 24-hour randomization with allocation concealment, data input, data cleansing, and data export for statistical analysis.

Data will be collected by means of electronic case report forms via the Internet using the IEP-HCor Data Management System. Data are entered into the system by each center team. All forms are electronically signed by the principal investigator in each center or by other appointed persons. Instructions for using the system will be made available to investigators.

Ensuring Quality of Data

The procedures to ensure data quality include:

1) All investigators will attend a training session before the start of the study to standardize procedures, including data collection;
   a. Training sessions on the completion of the checklists, tools of clinician prompting, and patient records will be provided for the ICU team;
   b. The training of the health professional who is not involved in the care of ICU patients and who will collect much of the information from the medical records will be held during a separate session;
2) The investigators will be able to contact the Study Coordinating Center to solve issues or problems that may arise;
3) Data entry into the IEP-HCor Data Management System is subject to various checks for missing data, plausible, possible or non-permitted value ranges, and logic checks. Problems are informed by the system at the time of data entry;
4) All data entered into the system will be reviewed by the Coordinator of Data Management of the study using the IEP-HCor, who will send any requests for correction to the investigators;
5) Statistical techniques to identify inconsistencies will be applied periodically (about every two weeks). The centers will be notified of the inconsistencies and asked to correct them;
6) Statistical routines to identify fraud will be conducted periodically (every 90 days);
7) The Coordinating Center will conduct a monthly review of detailed reports on screening, inclusion, follow-up, and data consistency and completeness. The Coordinating Center will take immediate action to solve any problems;

8) The primary outcome of the study, in-hospital death, does not need to be adjudicated;

9) The adjudication, conducted by a blinded independent committee, will be held only for the diagnosis of VAP and CLABSI.

**Statistical Considerations**

**Sample Size**

Phase II will include at least 102 ICUs and 60 patients per unit.

With 102 ICUs and average of at least 50 patients per unit, the study will have a power of 90% and a type I error of 5% to detect an absolute reduction in in-hospital mortality of 6% (from 30% in the control group to 24% in the experimental group), considering a coefficient of variation (K) of 0.25, and appropriate analysis adjusted for cluster effect. The sample size may be adjusted after analyzing the in-hospital mortality rate and the coefficient of variation (K) in the database (phase I).

It is possible that part of the participating ICUs will not able to perform the individual data collection of at least 50 patients in Phase I. These ICUs will not participate in the other phases of the study. We estimate that up to 33% of the units participating in Phase I will not qualify to participate in the other phases. Thus, to ensure a minimum of 102 ICUs participating in Phase II, we intend to include 152 ICUs in Phase I.

**Statistical Analyses**

Statistical analyzes will be conducted following the principle of "intention-to-treat". Thus, the observations of the ICUs will be analyzed according to the group to which they were allocated (e.g., experimental ICU analyzed the intervention group), even if there is nonadherence or data crossover of part or the whole unit.

Normality will be assessed using visual inspection of histograms and the D'Agostino-Pearson’s normality tests. Baseline characteristics will be expressed as counting (%), means (SD), or median (IQR), whenever appropriate, for the intervention and control groups using both individual or cluster variables.

In our primary analysis to assess the effect of study interventions on in-hospital mortality truncated at 60 days, we will use random effects logistic regression, considering a fixed effect intercept for the strata and adjusting for ICUs' standardized mortality ratio (calculated with SAPS 3) observed in the observational phase and patients’
SAPS 3 score observed in the randomized phase (Table 3). Random intercept and slope of treatment effects will be used to account for the correlation of patients’ observations within clusters.

Secondary outcomes with binary, continuous or count features will be adjusted by generalized linear mixed models considering the appropriate distributions (binomial, Poisson, Negative binomials models, Gamma, Normal), (Table 4). In all analyses we will adjust for baseline values of the outcome variables at the ICU level determined in the observational phase.

We do not expect substantial loss to follow-up for the primary outcome data, in-hospital mortality. However, if there are cases of losses to follow-up, we will attribute data using multiple imputation techniques. For all other outcomes, we will analyze only those patients with complete data (complete case analysis).

All significance probabilities (p values) presented will be bilateral and values lower than 0.05 will be considered statistically significant. The statistical analysis will be performed using the R(R Core Team, 2014).

Analysis of Subgroups

We will carry out analyses of the effect of the intervention on the primary outcome according to the following subgroups: two strata of baseline in-hospital mortality (by median) observed for ICUs in the observational preparatory phase; public or private hospital; medical versus surgical patient; two strata of the SOFA score; presence of sepsis at admission; need of mechanical ventilation at admission. We will explore how treatment effect varies by patients’ baseline risk of death (estimated by baseline SAPS3) in a more detailed fashion. That is, we will assess treatment effect on in-hospital mortality according to patients’ baseline SAPS3 grouped in deciles. We will also assess whether treatment effect varies according to baseline scores for each of the six SAQ domains determined for ICUs in the observational preparatory phase. Subgroup analysis will be performed irrespective of intervention efficacy. We will assess the statistical significance of subgroup effects by formal tests of interaction.

Multiple Mediation Models

We will use multiple mediation models to quantify the indirect effects of the use of checklists and clinician prompting on mortality mediated by the target care processes of the checklist and changes in the safety culture. Figure 1 shows a schematic representation of the multiple mediation model. The potential mediators considered are the secondary outcomes that reflect the target care processes of the checklist and the score on the Safety Attitudes Questionnaire (demonstrating safety culture).

We will use the bootstrapping technique to test multiple mediation models, an alternative technique to the Baron and Kenny's causal steps model to evaluate mediation.28 Bootstrapping analysis has a higher power, minimizes the number of statistical tests, quantifies the effects of the mediation, and does not assume that the indirect effects are normally distributed.29 This technique will be implemented using a macro for the SPSS developed by
Preacher and Hayes, which allows you to analyze models with dichotomous outcome. We will generate 5,000 resampling by means of bootstrap to generate 95% confidence intervals.

Figure 1. Mediation of the effects of the implementation of checklists during daily multidisciplinary visits and clinician prompting on in-hospital mortality through care processes affected by the checklist and safety culture.

Arrows $a^1$ to $a^9$ represent the direct effect of the independent variable (checklists and clinician prompting) on the potential mediators. Arrows $b^1$ to $b^9$ represent the direct effect of potential mediators on the dependent variable (in-hospital mortality). The product $a^1 b^1$ to $a^9 b^9$ represents the indirect effect of the independent variable through each potential mediator on the independent variable. $c'$ represents the direct residual effect of the use of checklists and clinician prompting on hospital mortality.
Ethical Aspects and Good Clinical Practices

The study will be carried out in accordance with national and international resolutions described in the following documents:

- Resolution no. 466, December 12, 2012 and additional rulings by the National Health Council/Ministry of Health;
- Helsinki Declaration and all its revisions and changes;
- Document of the Americas.

Study Approval

Before starting the study, the investigator shall forward a copy of the protocol and other required statements to the Research Ethics Committee (REC) of each participating institution. A covering letter and an approval letter from the REC, if approval is obtained, shall be forwarded to the Coordinating Center. Additionally, all amendments to the protocol shall be approved by the REC of each participating center.

Institutional Approval

We will require institutional approval provided by the signature of the Institutional Approval Form in order to conduct the study. The Institutional Approval Form shall be analyzed and approved by the REC, and signed by the Director of each participating institution and the coordinator of the ICU. Appendix B shows the institutional approval form.

Obtaining the informed consent (IC) raises logistical and methodological problems in studies of improvement of healthcare quality using cluster randomization. The main problems are described below:

1) Intervention is not directed to patients, instead it is intended to health professionals; therefore, it can be difficult to prevent that the intervention (checklist) is applied to individuals. The individual consent would relate only to data collection, not to the intervention;

2) When the teams working in the units (ICUs) are large, obtaining IC can be hardly feasible;

3) The individual consent may generate bias in the study results, having a negative impact on the care provided for future patients. In the present study in particular, there will not be any direct intervention or assessment of procedures that are not properly assessed and
recognized by clinical practice, and we will only collect data of overall outcome of care in each institution. In these cases, it is recommended to obtain consent from the person responsible for the institution, with no need to get individual IC.\textsuperscript{30-33} Based on the reasons mentioned above, we request exemption from obtaining IC in this study.

**Informed Consent**

We will obtain written informed consent from ICU healthcare personnel before asking them to fill in the Safety Attitudes Questionnaire in both phases I and II. The request for consent and relevant information for the study should be conducted by the professional responsible for collecting data from each center.

The consent form must be signed and dated by the research subject and investigator in duplicate and initialed on every page. A copy of the consent form must be given to the research subject and the other must be filed with the other study documents. It will be clearly explained to research subjects that their participation is voluntary and that they may withdraw from the study at any time without any implication on the quality. Appendix E shows the consent form.

**ICU and Hospital Data Confidentiality**

Data collection for characterization of hospitals and ICUs will be performed anonymously so that the units cannot be identified later. Data will be reported in an aggregate manner. Appendix B shows the institutional approval form including information regarding data confidentiality.

Data on the ICUs will not be provided to third parties, including funders of the study or regulatory agencies.

**Patient Data Confidentiality**

Patient identification data will not be submitted to the Coordinating Center of the Study. Each patient and research center is identified in the electronic case report form by a unique number. Information obtained from medical records should be handled as confidential data by the research centers; it must be kept in restricted access locations and anonymity must be ensured on interim and final reports.

**Progress Reports**
Investigators must submit written summaries of the status of the study to their Institution’s REC every six months, as well as a final report at the end of the study.

**Study Organization**

**Study Sponsors and Coordinators**

The teams of the Research Institute at Hospital do Coraçao (IEP-HCor), D’Or Institute for Research and Education (IDOR), Hospital Samaritano São Paulo and Hospital Moinhos de Vento are the sponsors and coordinators of the study. The coordinators are assisted by research managers, data management team including computer systems analysts and data quality control analysts, and statisticians.

The Coordinating Centers are responsible for:

- Planning and conducting the study:
  - Designing the protocol;
  - Designing the electronic case report forms (e-CRF);
  - Designing the operation guide;
  - Managing and controlling data quality: Designing, testing, and maintaining the electronic data capture system; Continuous data quality control;
  - Assisting the Steering Committee;

- Managing the research centers:
  - Selecting and training the research centers;
  - Helping the centers prepare a regulatory report to be submitted to the RECs and assisting the centers with the submission;
  - Monitoring recruitment rates and the actions to increase recruitment;
  - Monitoring follow-up and implementing actions to prevent follow-up losses;
  - Monitoring visits;
  - Sending study materials to the research centers;
  - Producing a monthly study newsletter;
  - Developing supporting material for the study;

- Statistical analysis and helping to write the final manuscript:
  - Complete statistical analysis;
  - Helping to write the final manuscript.
Institutional support from the Brazilian Association of Intensive Care Medicine – AMIB and the Brazilian Research in Intensive Care Network – BRICNet

The AMIB supports the CHECKLIST-ICU TRIAL study by means of the AMIB-Net. The AMIB-Net is a group of critical care physicians (intensivists) organized and coordinated by the AMIB that aims to assist in the development and performance of collaborative clinical research to improve the outcome of critically ill children and adults. The support from the AMIB-Net will be provided by the invitation to the intensivists registered on the network. In addition, the AMIB-Net will facilitate the organization of meetings of investigators by taking advantage of national scientific events organized by the AMIB.

The Brazilian Research in Intensive Care Network - BRICNet, is a independent and collaborative Brazilian network focused on the performance of clinical studies in the field of intensive care medicine. The BRICNet will assist in the selection and invitation of the centers to participate in the CHECKLIST-ICU Trial.

Steering Committee

The Steering Committee is responsible for the overall study supervision, assisting in developing the study protocol and preparing the final manuscript. All other study committees report to the Steering Committee. The Steering Committee members are investigators trained in designing and conducting randomized clinical trials, intensivists, and epidemiologists experienced in conducting multicenter randomized studies.

The members of the Steering Committee are:

- Alexandre Biasi Cavalcanti, MD, PhD. Epidemiologist and intensivist. Coordinator of Research Initiatives at the IEP-HCor, São Paulo - SP.
- Flávia Machado, MD, PhD. Intensivist. Associate professor and head of the Department of Intensive Care, Course of Anesthesiology, Pain and Intensive Care, Universidade
Federal de São Paulo. Vice President of the Latin American Sepsis Institute (ILAS). Editor-in-chief of the Revista Brasileira de Medicina Intensiva, related to the Brazilian Association of Critical Care Medicine.

- Derek Angus, MD, MPH, FRCP. Chair, Department of Critical Care Medicine. The Mitchell P. Fink Endowed Chair in Critical Care Medicine. Professor of Critical Care Medicine. Medicine Health Policy and Management and Clinical and Translational Science. University of Pittsburgh School of Medicine and Graduate School of Public Health

- Valquiria Pelisser Campagnucci, MD. Cardiovascular Surgery. Coordinator of the Adult-ICU, Hospital Samaritano, São Paulo-SP.

- Patricia Vendramim. Nurse, Advisor for Scientific Research of the Hospital Samaritano, São Paulo – SP.

- Cassiano Teixeira, MD, PhD. Intensivist, Adult ICU, Hospital Moinhos de de Vento, Porto Alegre – RS.

- Edson Romano, MD. Cardiologist and intensivist. Coordinator of the Adult ICU-HCor, São Paulo – SP.

- Karina Normilio da Silva. Researcher of the IEP-HCor, São Paulo - SP.

- Viviane Caetano Chiattone. Researcher of the IEP-HCor, São Paulo-SP.

- Hélio Penna Guimarães, MD, PhD. Assistant Physician, Clinical Practice Course of Federal University of São Paulo (UNIFESP), and attending physician at the Medical Clinic ICU at Hospital São Paulo - UNIFESP, São Paulo - SP.

- Otávio Berwanger, MD, PhD. Epidemiologist. Director of the IEP-HCor, São Paulo - SP.

Responsibilities of Investigators and Co-Investigators at Participating Centers

The principal investigator at each center will lead and/or supervise the daily operation of the project at his/her participating center and may appoint a co-investigator and a Research Coordinator. Most tasks can be delegated by the principal investigator to research professionals at the participating center, provided that the professionals are qualified for such tasks and that the delegation is clearly recorded, with the name of the professionals and their roles. However, the principal investigator is legally responsible for the study.

The principal investigator is responsible for:
1. Getting approval from the research ethics committee and forwarding the approval to the Coordinating Center of the Study; ensuring that approval is obtained before the beginning of recruitment;

2. Ensuring compliance with the protocol;

3. Ensuring that all ICU professionals involved in patient care are aware of and informed about the study;

4. Ensuring that all eligible patients are entered into the Data Management System of the Study and that protocol interventions are properly implemented;

5. Ensuring that data are properly collected and entered into the Study Data Management System.

**Event Adjudication Committee**

CLABSI and UTI are defined according to the 2008 Centers for Disease Control and Prevention (CDC)\(^4\) and National Healthcare Safety Network criteria. VAP is defined according to the 2013 CDC criteria.\(^5\)

Daily data for the surveillance of ventilator-associated events of all patients on mechanical ventilation are sent to the Coordinating Center on a standardized form. Based on these data, a research nurse on the Coordinating Center identifies cases of VAP. Those cases are adjudicated by a blinded intensivist from the Coordinating Center.

Investigators send the results of all blood cultures from patients with venous central lines to the Coordinating Center, and in case of positive cultures, information regarding other criteria for CLABSI (whether there are other probable sites for the infection, and for skin contaminants, whether there are signs and symptoms and how many blood cultures are positive for the same microorganism) is also sent. CLABSI cases are also adjudicated in a process similar to that of the VAP cases.

**Data Monitoring Committee**

There will not be a Data Monitoring Committee in this study, because this is a research of improvement of healthcare quality. The interventions are tools to increase the use of well-established evidence. Finally, there is no expectation that the proposed intervention can have a negative impact on the clinical evolution of the participants.
Rules for Termination of Participating Centers

After the ethical approval, the participating ICUs have six months to include and complete the follow-up of 60 patients in each study phase. Those ICUs that do not complete these activities in any of the phases will not participate in the main publication.

Publication Policy

The Steering Committee of the CHECKLIST-ICU Trial is responsible for publishing the study’s findings, whatever they are. Because the CHECKLIST-ICU Trial is a large-scale, collaborative, cluster randomized study, we intend to submit the main manuscript to high-impact journals (e.g., New England Journal of Medicine, The Lancet or JAMA). All efforts should be done to reduce the time between the closure of the database and the submission for publication.

Additionally, we intend to submit in two additional manuscripts the study protocol and the data of characterization of the ICUs according to the criteria of the RDC no. 7/2010 and RDC no. 26/2012.

The success of the study will depend on the team, the collaborative efforts of investigators, research coordinators, and multidisciplinary team of the ICUs. Thus:

- The main publication will be published on behalf of the group (ICU CHECKLIST-Trial Investigators).
- Up to three investigators from each center will be mentioned as collaborators in the end of the published manuscripts or in supplementary material, depending on the editorial policy of each journal. Names will be listed following the alphabetical order of center names.

Suggestions of topics for sub-studies and secondary publications must be submitted by the investigators to the Steering Committee, which will assess the proposal and may approve it, suggest improvements, or reject it. The evaluation will be conducted on the basis of scientific merit and contribution of investigators for the success of the main study.

The data obtained in the study belong to the coordinating centers/sponsors. Full or partial provision of the database to third parties will be carried out only after agreement of the four sponsoring institutions.
Conflicts of Interest Statement

The teams of the Research Institute at Hospital do Coração (IEP-HCor), D’Or Institute for Research and Education (IDOR), Hospital Samaritano de São Paulo and Hospital Moinhos de Vento are the sponsors and coordinators of the study, whose only purpose is to improve the quality of care provide to the patients admitted to ICUs in Brazil. There are not conflicts of interest with manufacturers or the project funders (BNDES and PROADI).

Potential Benefits of the Study

If this study finds that the implementation of the interventions, including the use of checklist during daily multidisciplinary visit and clinician prompting, is able to improve the results, i.e., to reduce mortality and/or other relevant outcomes for patients, these interventions might be widely used in intensive care medicine, even in settings with limited resources.
References


24. PROC GENMOD with GEE to analyze correlated outcomes data using SAS. Proceedings of the Western Users of SAS Software Fourteenth Annual Conference; 06 Sep 27; 2006.


