A cluster-randomised trial of a multifaceted quality improvement intervention in Brazilian intensive care units (Checklist-ICU trial): statistical analysis plan

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ABSTRACT

Background: The Checklist During Multidisciplinary Visits for Reduction of Mortality in Intensive Care Units (Checklist-ICU) trial is a pragmatic, two-arm, cluster-randomised trial involving 118 intensive care units in Brazil, with the primary objective of determining if a multifaceted quality-improvement intervention with a daily checklist, definition of daily care goals during multidisciplinary daily rounds and clinician prompts can reduce inhospital mortality.

Objective: To describe our trial statistical analysis plan (SAP).

Methods: This is an ongoing trial conducted in two phases. In the preparatory observational phase, we collect three sets of baseline data: ICU characteristics; patient characteristics, processes of care and outcomes; and completed safety attitudes questionnaires (SAQs). In the randomised phase, ICUs are assigned to the experimental or control arms and we collect patient data and repeat the SAQ.

Results: Our SAP includes the prespecified model for the primary and secondary outcome analyses, which account for the cluster-randomised design and availability of baseline data. We also detail the multiple mediation models that we will use to assess our secondary hypothesis (that the effect of the intervention on inhospital mortality is mediated not only through care processes targeted by the checklist, but also through changes in safety culture). We describe our approach to sensitivity and subgroup analyses and missing data.

Conclusion: We report our SAP before closing our study database and starting analysis. We anticipate that this should prevent analysis bias and enhance the utility of results.

Crit Care Resusc 2015; 17: 113–121

Human error is inevitable, especially with fatigue or stress.[1] Checklists have long been used in aviation and other high-risk settings such as nuclear plants and oil drilling platforms to reduce errors of omission and promote an environment of improved teamwork.[2,3] Several recent studies have reported successful cases of checklist implementation in health care areas. Some influential examples are the Safe Surgery Checklist[4] and the Keystone Intensive Care Unit Project to prevent central line-associated bloodstream infection (CLABSI).[5,6] However, adoption in health care areas has been slower than in other fields due to strong cultural factors such as a perception that the use of checklists would denote a lack of medical skill or knowledge, or that checklists limit medical decision making.[3] Additionally, the evidence on the effectiveness of checklists is based mostly on simple before-and-after studies, and results are not consistent.[7,8]

We hypothesise that a multifaceted intervention, including systematic use of a checklist with definition of daily goals during multidisciplinary ICU daily rounds and clinician prompting, can decrease inhospital mortality of critically ill patients. Our secondary hypothesis is that the ICU daily round checklist with clinician prompting will decrease mortality, not only through improvement in care processes targeted by the checklist, but also through improvement in safety culture. We believe that the study intervention may decrease the power distance ("flatten hierarchy") and give voice to junior members of the team. This means more people will contribute and any potential error of a senior team member is more likely to be corrected.

Here we outline the statistical analysis plan (SAP) for the Checklist During Multidisciplinary Visits for Reduction of Mortality in Intensive Care Units (Checklist-ICU) trial, with the aim of preventing statistical analysis bias arising from exploratory analyses after study results are known.[9] The SAP was developed by the study statisticians and the chief investigator in consultation with a senior statistician, and was revised by members of the steering committee.

Study objectives

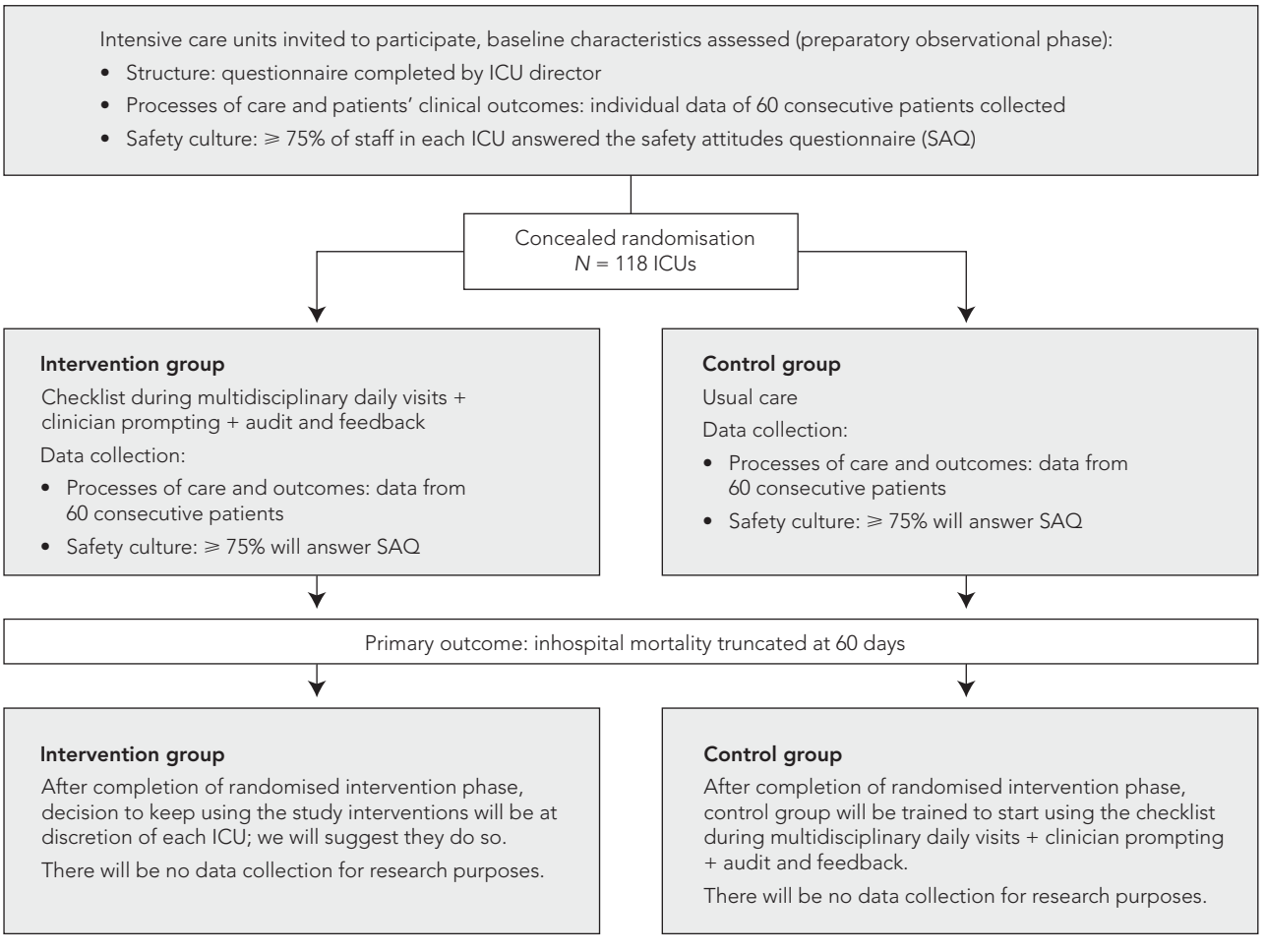
Primary objective

Our primary objective is to assess whether the use of a multifaceted quality improvement intervention, including checklists and definition of daily care goals during multidisciplinary rounds, as well as clinician prompting, can improve the inhospital mortality of patients admitted to ICUs.

Secondary objectives

Our secondary objective is to assess the effects of the study intervention on care processes, clinical outcomes and safety

Figure 1. Study design



culture. If we find a reduction in inhospital mortality, we also aim to better define the factors that mediate improvements in clinical outcome, ie, whether the benefit is mediated only through improved compliance with the processes targeted by the checklist or also through improvements in safety culture and flattening of hierarchy.

Overview of trial design

Design

The Checklist-ICU trial is a pragmatic, two-arm, cluster-randomised trial involving 118 ICUs in Brazil to determine the effectiveness of a multifaceted quality improvement intervention to reduce inhospital mortality (Figure 1). The full study protocol was published elsewhere[10] and is registered at www.ClinicalTrials.gov (NCT01785966).

We are conducting the study in two phases: a preparatory observational phase and a randomised phase. In the preparatory observational phase we are collecting baseline data to characterise our sample, obtain outcome data for the stratified randomisation and for adjusting multivariate analyses for baseline rates of clinical outcomes. In the next phase, we are randomising ICUs to the experimental or control arm. The unit of concealed randomisation is the ICU, to minimise contamination, as we are intending to apply the intervention to the whole ICU multidisciplinary team. Randomisation is stratified according to the median of baseline inhospital mortality, determined in the observational preparatory phase. ICUs assigned to the experimental arm receive a multifaceted intervention comprising the systematic application of a checklist with definition of daily goals during daily multidisciplinary visits, and using prompting by clinicians. The 11-item checklist is read aloud by a nurse during the daily round and answered by members of the multidisciplinary team. During the discussion of each patient's case, the lead doctor takes note of daily care goals on a standard form and reads them to the team. Every afternoon, a nurse checks whether daily care goals were

Figure 2. Daily rounds checklist

CHECKLIST ICU Trial

DAILY CHECKLIST

Date: ☐☐/☐☐/☐☐☐☐

Item	Status			Actions / remarks
Is nutrition adequate?	☐ Yes	☐ No	☐ NA/CI	
Venous thromboembolism prophylaxis ordered?	☐ Yes	☐ No	☐ NA/CI	
Head of bed is at 30° or more?	☐ Yes	☐ No	☐ NA/CI	
Does the patient meet criteria for new severe sepsis/septic shock?	☐ Yes	☐ No	☐ NA/CI	
Is there indication to start, adjust or stop antibiotics?	☐ Yes	☐ No	☐ NA/CI	
Is it possible to remove central line?	☐ Yes	☐ No	☐ NA/CI	
Is it possible to remove Foley catheter?	☐ Yes	☐ No	☐ NA/CI	
Is analgesia adequate?	☐ Yes	☐ No	☐ NA/CI	
Is it possible to reduce sedatives?	☐ Yes	☐ No	☐ NA/CI	
Is a spontaneous breathing trial possible?	☐ Yes	☐ No	☐ NA/CI	
What is the PaO2/FiO2? What is the tidal volume per kg of predicted body weight?				

ICU = intensive care unit. NA = not applicable. CI = contraindicated.

accomplished and prompts the doctor if there are pending items. ICUs assigned to the control arm maintain usual care.

Eligibility criteria

We are including ICUs that admit adult patients and conduct (or wish to conduct) multidisciplinary daily rounds with at least a doctor and a nurse on all working days. We invited all members of the Brazilian Research in Intensive Care Network (BRICNet), the Associação Brasileira de Medicina Intensiva (Brazilian Intensive Care Association) (AMIB) and AMIB-Net to participate in the trial. ICUs that admit exclusively cardiac patients, step-down units, and ICUs that already systematically use multiple-item checklists during multidisciplinary daily visits are being excluded. For the randomised phase, we are including only ICUs that successfully collect data in the observational phase (those that include $\geqslant 40$ patients within 6 months and apply the safety attitudes questionnaire [SAQ] to $\geqslant 75\%$ of their staff). Previous studies have obtained response rates for the SAQ of 48%–67%.[11,12] In order to minimise bias, we demand a response rate of at least 75% for the SAQ so that our worst-case scenario would still be better than previous studies.

We are including 60 consecutive patients over 18 years with lengths of ICU stay longer than 48 hours (patients with lengths of stay less than 48 hours are unlikely to be affected by the study interventions). Patients can be included only once in the study. We are excluding patients with high probabilities of early death between the 48th and 72nd hour of their ICU stay, patients admitted only for palliative care and those with a suspected or confirmed diagnosis of brain death.

We anticipate that most of the potential benefit of checklists will be observed in patients who have a longer ICU stay, and are thus more vulnerable to developing complications such as mechanical ventilator-associated events, CLABSI or venous thromboembolism (VTE). We therefore decided to enrol only patients with an ICU stay of longer than 48 hours to increase our likelihood of detecting a potential effect of the quality improvement intervention on clinical outcomes. Patients with shorter lengths of stay are admitted to the ICU mainly for monitoring or are extremely sick cases who would die as a result of the cause of their ICU admission.

Description of intervention

The intervention comprises the use of checklists and daily goals definition during daily multidisciplinary rounds, as well as clinician prompting, for all patients during their whole ICU stay. The daily rounds checklist was developed following the five steps detailed previously[10] and adapted from the practice guidelines development cycle.[13] The final version of the checklist contains 11 items (Figure 2).

The checklist is read aloud by a nurse and answered by participants on multidisciplinary rounds on weekdays (at least). Additionally, daily goals are written in a standardised form and read aloud to the team. Every afternoon, a nurse reviews the daily goals, and prompts the on-call doctor if there are pending items. The ICUs randomised to the control arm maintain usual care.

Outcomes

The primary outcome is inhospital mortality, truncated at 60 days. Only deaths occurring after 48 hours of ICU admission are considered because only patients staying in the ICU longer than 48 hours are included.

We are assessing secondary outcomes that indicate adherence to processes of care, patients' clinical results and safety culture. The secondary outcomes that show adherence to the appropriate care processes are:

- head of bed elevated at 30° in eligible patients

Table 1. Summary of patient data collected

Case report form	Data
Baseline	Date of birth, sex, height, dates of hospital and ICU admission, data for the SAPS 3 and SOFA scores, main category of disorders that prompted the ICU admission
Daily ICU visit (Day 2 to Day 17)	Daily multidisciplinary visit
	Adherence to study protocol: completed checklist (only for experimental-arm ICUs), completed clinician-prompting form (only for experimental-arm ICUs)
	Processes of care: head of bed elevated to 30°, receiving enteral or parenteral feeding, adequate prevention of venous thromboembolism, antibiotic use, adequate sedation (RASS score, – 3 to 0) and tidal volume for patients on MV, use of central line catheter, use of indwelling urinary catheter
	Clinical outcomes: new CLABSI, new VAP, new urinary tract infection associated with catheter, need for MV
ICU and hospital discharge	ICU and hospital discharge truncated at 60 days: date of ICU discharge, vital status at ICU discharge, date of hospital discharge, vital status at hospital discharge, number of days on MV during ICU stay
VAP	For patients on MV for ⩾ 4 days, daily data to assess CDC criteria for VAP
CLABSI	CDC criteria

ICU = intensive care unit. SAPS = Simplified Acute Physiology Score. SOFA = Sequential Organ Failure Assessment. RASS = Richmond Agitation–Sedation Scale. MV = mechanical ventilation. CLABSI = central-line associated bloodstream infection. VAP = ventilator-associated pneumonia. CDC = Centers for Disease Control and Prevention.

- adequate prevention of VTE
- rate of central line catheter use
- rate of indwelling urinary catheter use
- patient-days under light sedation or alert and calm (Richmond Agitation Sedation Scale – 3 to 0) in patients on mechanical ventilation (MV)
- tidal volume ⩽ 8 mL/kg in patients on MV
- number of patients receiving enteral or parenteral feeding.

We chose these care processes as they are associated with relevant outcomes for patients and because they are targeted by the daily round checklist.

The secondary outcomes that reflect clinical results are:

- ICU mortality
- MV-free days between Day 1 and Day 28
- central line-associated CLABSI rate
- ventilator-associated pneumonia (VAP) rate
- urinary tract infection (UTI) rate
- length of ICU stay
- length of hospital stay.

Length of ICU stay and length of hospital stay are being truncated at 60 days. VAP is defined according to the 2013 Centers for Disease Control and Prevention (CDC) criteria.[14] CLABSI and UTI are also defined according to CDC criteria.[15] ICU mortality and length of ICU stay are determined at the discharge after the first ICU admission.

We use the validated Brazilian–Portuguese version of the SAQ to assess safety culture.[12,16] This version of the SAQ has 36 questions divided into six domains: teamwork climate, safety climate, perceptions of management, job satisfaction, working conditions, and stress recognition. The perceptions of management domain may be further divided into perceptions of hospital management and perceptions of ICU management.

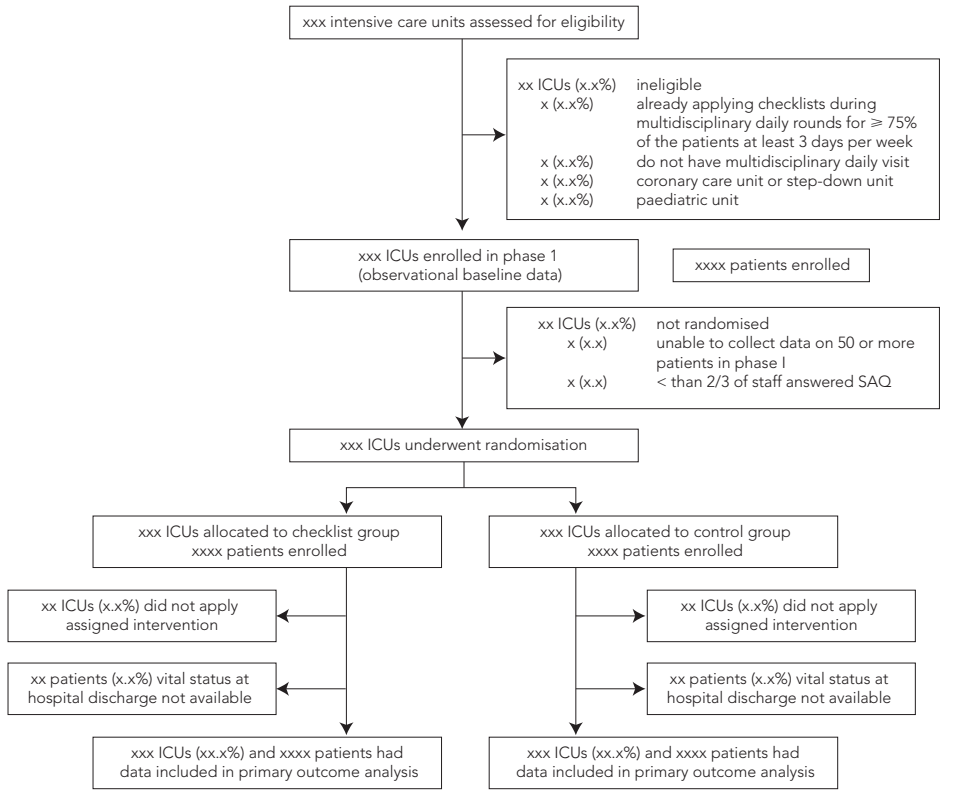
Sample size

We plan to include at least 102 ICUs and 60 patients per ICU. With 102 ICUs and an average of 50 patients per unit, the study has a power of 90% to detect an absolute reduction of 6% in inhospital mortality, truncated at Day 60. This reduction is from 30% in the control arm to 24% in the experimental arm. The study has a type I error level of 5% with a coefficient of variation (*k*) of 0.25.[17] We estimate inhospital mortality of 30% in the control group, using data on patients with lengths of ICU stay longer than 48 hours, extracted from a large administrative database (Epimed Monitor System, Epimed Solutions) for several hundred ICUs in Brazil. We consider that a 20% relative risk reduction (6% absolute risk reduction) is clinically relevant and biologically plausible an the effect size typically observed in health care interventions.[18]

We have no previous data on between-cluster variance of inhospital mortality tfor estimating *k*. We therefore used a conservative value of 0.25, which represents a moderate-to-large variation between ICUs.[17] This value of 0.25 means that 95% of true cluster inhospital mortality rate lies between 15.3% and 44.7% for the control group. Furthermore, as our randomisation is stratified by baseline inhospital mortality of the ICUs, we expect that the final *k* value will be lower.

For the randomised phase, we are including only ICUs that successfully collect data in the observational phase, for

Figure 3. Study flow



SAQ = safety attitudes questionnaire.

⩾ 40 patients within 6 months, and that apply the SAQ to ⩾ 75% of their staff. Because we anticipate that up to one-third of ICUs would be unable to collect the necessary data, we included 152 ICUs in the preparatory observational phase, to finish with at least 102 ICUs participating in the randomised phase (118 ICUs met the criteria to be enrolled in this phase).

Datasets

We have three separate datasets: one describing characteristics of ICUs; a second with patient characteristics, processes of care and clinical outcomes; and the third with ICU staff answers to the SAQ.

ICU characteristics

We describe the ICUs according to medical device regulations 7/2010 and 26/2012, which are standards from the Brazilian Health Surveillance Agency (ANVISA) with minimum requirements for the operation of ICUs. We collect 92 variables describing several ICU characteristics related to human resources, health care resources, infrastructure, equipment, care protocols, quality-of-care measures, transport of patients, prevention of health care-related infections, risk management and family policies. The characteristics of each unit are being treated confidentially and the data will be reported in an aggregate manner.

Patient characteristics, processes of care and clinical outcomes

Data from 60 consecutive eligible patients are collected in the baseline observational phase and again in the randomised phase. A trained health care professional who does not provide care for ICU patients collects daily data over 15 days, from Day 2, the day the patient is enrolled, until Day 17. We are limiting daily data collection to a 15-day period because most clinical outcomes are probably concentrated in this period, and obtaining daily data for longer would not be feasible. Table 1 shows a summary and time schedule of the patient data.

Safety culture

All health care professionals (eg, doctors, nurses, clinical nurses, respiratory therapists, nutritionists, psychologists, speech therapists, pharmacists, occupational therapists and social workers) in the participating ICUs are invited to complete the SAQ. We ask the principal investigators to indicate the number of professionals at their ICUs. In order to promote a high level of staff participation and encourage unbiased and truthful answers to the SAQ, we assure complete anonymity, so we do not record names or identification codes in the questionnaires. Our goal is to obtain completed SAQs from at least 75% of staff members.

Statistical analysis

Principles

All statistical analyses will be conducted according to the intention-to-treat principle. The ICU data will be analysed according to the arm to which they were allocated, even if

Table 2. Baseline characteristics of ICUs and patients

Characteristic	Intervention arm	Control arm
ICU characteristics		
Number of beds, median (range)	xx (xx–xx)	xx (xx–xx)
Surgical, *n* (%)	xxx (xx.x%)	xxx (xx.x%)
Medical, *n* (%)	xxx (xx.x%)	xxx (xx.x%)
Mixed (medical and surgical), *n* (%)	xxx (xx.x%)	xxx (xx.x%)
Hospital type, *n* (%)		
Public	xxx (xx.x%)	xxx (xx.x%)
Academic*	xxx (xx.x%)	xxx (xx.x%)
Number of hospital beds, median (range)	xxx (xxx–xxx)	xxx (xxx–xxx)
Number of ICU beds/hospital beds, mean (SD)	x.xx (xx)	x.xx (xx)
Patient characteristics†		
Mean age, years (SD)	xx.x (xx.x)	xx.x (xx.x)
Female, *n* (%)	xxx (xx.x%)	xxx (xx.x%)
Type of admission, *n* (%)		
Medical	xxx (xx.x%)	xxx (xx.x%)
Elective surgery	xxx (xx.x%)	xxx (xx.x%)
Emergency surgery	xxx (xx.x%)	xxx (xx.x%)
Reason for ICU admission, *n* (%)		
Postoperative care	xxx (xx.x%)	xxx (xx.x%)
Sepsis	xxx (xx.x%)	xxx (xx.x%)
Respiratory failure (except sepsis)	xxx (xx.x%)	xxx (xx.x%)
Shock (except sepsis)	xxx (xx.x%)	xxx (xx.x%)
Neurological	xxx (xx.x%)	xxx (xx.x%)
Cardiovascular	xxx (xx.x%)	xxx (xx.x%)
Gastrointestinal	xxx (xx.x%)	xxx (xx.x%)
Haematological	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)
Comorbidities		
Metastatic or haematological cancer, *n* (%)	xxx (xx.x%)	xxx (xx.x%)
Cirrhosis, *n* (%)	xxx (xx.x%)	xxx (xx.x%)
AIDS, *n* (%)	xxx (xx.x%)	xxx (xx.x%)
SAPS 3 score at admission, mean (SD)	xx.x (xx.x)	xx.x (xx.x)
SOFA score at admission, mean (SD)	xx.x (xx.x)	xx.x (xx.x)

ICU = intensive care unit. SAPS = Simplified Acute Physiology Score. SOFA = Sequential Organ Failure Assessment. * Hospitals that provide training for medical students. † Obtained at randomised phase.

part of or the whole unit is nonadherent. Our primary analysis will be patient-level analysis, although we will also carry out cluster-level sensitivity analyses.

Normality will be assessed by visual inspection of histograms and D'Agostino–Pearson normality tests.[19] For the experimental and control arms, baseline characteristics will be expressed as counts and percentages, means and standard deviations, or medians and interquartile ranges, whenever appropriate, using individual or cluster variables.

The tables will focus on comparisons of data from the randomised phase. The difference in outcome rates from baseline to the randomised phase in both arms will be shown in Appendix tables. Here we include mock tables and figures.

All hypothesis tests will be two-sided, with an α of 5%. We will not adjust *P* for multiple comparisons. Analyses will be performed using the R program (R Development Core Team) and SAS version 9.3 (SAS Institute).

Trial profile

The flow of patients and ICUs through the trial will be shown as a Consolidated Standards of Reporting Trials algorithm (Figure 3).

Baseline comparisons

We will present characteristics of ICUs and baseline characteristics of patients by study arm, as shown in mock Table 2 and Appendix Table 1 (see cicm.org.au/Resources/Publications/Journal).

Adherence to study interventions

We will report use of the verbal checklist and clinician prompting in the intervention arm to assess adherence to the protocol. Multidisciplinary daily visits will be shown for both arms.

Effect on outcomes

In our primary analysis to assess the effect of study interventions on inhospital mortality, truncated at 60 days, we will use random-effects logistic regression,[20] with a fixed-effect intercept for the strata.[21] We will adjust for standardised mortality ratios of ICUs (calculated with the Simplified Acute Physiology Score [SAPS] 3) obtained in the observational phase and patient SAPS 3 scores obtained in the randomised phase (Table 3). Random-intercept and slope-of-treatment effects will be used to account for the correlation of patient observations within clusters.

Secondary outcomes with binary, continuous or count features will be adjusted by generalised linear mixed models, with the appropriate distributions (binomial, Poisson, negative binomials models, gamma and normal) (Table 3 and Table 4). In all analyses, we will adjust for baseline values of the outcome variables at the ICU level determined in the observational phase.

Table 3. Effect of the multifaceted intervention on the primary outcome and secondary clinical outcomes

Outcome	Intervention group	Control group	Effect estimate, intervention v control (95% CI)*	*P*
Primary outcome				
Inhospital mortality, *n*/total (%)*	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx (xxx to xxx)	x.xx
Secondary clinical outcomes				
ICU mortality, *n*/total (%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx (xxx to xxx)	x.xx
Catheter-related bloodstream infection, *n*/1000 patient-days	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx (xxx to xxx)	x.xx
Ventilator-associated pneumonia, *n*/1000 patient-days	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx (xxx to xxx)	x.xx
Urinary tract infection, *n*/1000 patient-days	xxx/xxx (xx.x)	xxx/xxx (xx.x)	xxx (xxx to xxx)	x.xx
Ventilator-free days in a 28-day period, mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xxx (xxx to xxx)	x.xx
ICU length of stay, mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xxx (xxx to xxx)	x.xx
Hospital length of stay, mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xxx (xxx to xxx)	x.xx

ICU = intensive care unit. * All effect estimates are adjusted for baseline values of outcome variables, except the primary outcome odds ratio which is adjusted for baseline values of ICU standardised mortality rate and patient Simplified Acute Physiology Score 3 scores.

Multiple mediation analysis (secondary hypothesis)

If inhospital mortality is decreased in the experimental group compared with the control group, 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. This will be a patient-level analysis considering patient-level variables (care processes and inhospital mortality) and ICU-level variables (treatment group and SAQ scores). Figure 4 is a schematic representation of the multiple mediation models. The mediators that will be considered are the secondary outcomes reflecting the target care processes of the checklist and the scores on the seven SAQ domains (demonstrating safety culture).

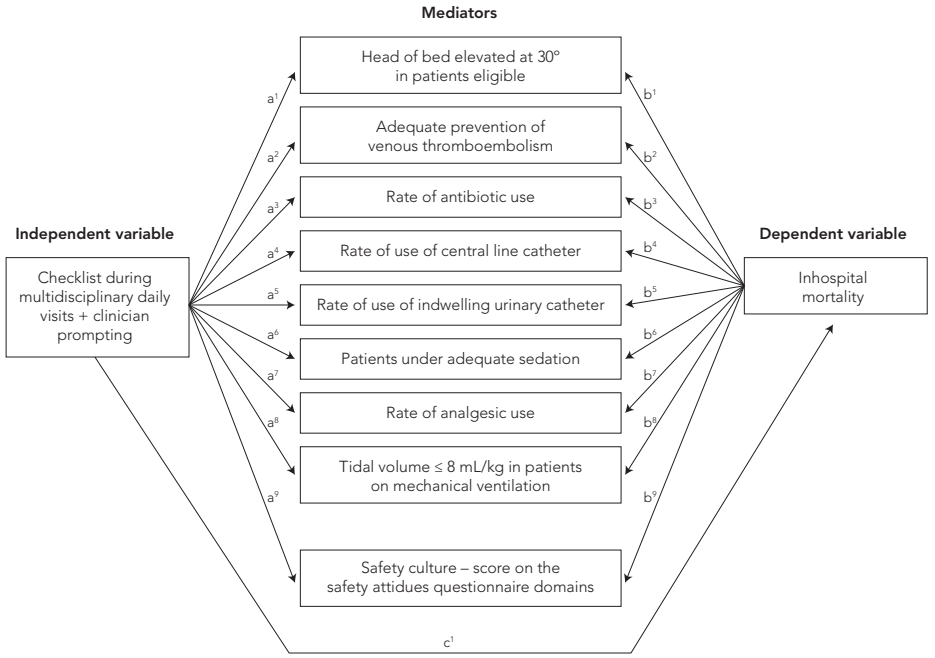
We will use the bootstrapping technique to test multiple mediation models, an alternative technique to the Baron and Kenny causal steps model to evaluate mediation.[22] Bootstrapping analysis has a higher power, minimises the

Table 4. Effect of the multifaceted intervention on secondary outcomes reflecting processes of care and safety culture

Outcomes	Intervention group	Control group	Intervention v control (95% CI)*	*P*
Processes of care				
Head of bed elevated ⩾ 30°†	xxxx/xxxx (xx.x%)	xxxx/xxxx (xx.x%)	x.xx (x.xx–x.xx)	x.xx
Adequate prophylaxis for venous thromboembolism†	xxxx/xxxx (xx.x%)	xxxx/xxxx (xx.x%)	x.xx (x.xx–x.xx)	x.xx
Adequate sedation (RASS score – 3 to 0)†	xxxx/xxxx (xx.x%)	xxxx/xxxx (xx.x%)	x.xx (x.xx–x.xx)	x.xx
Central venous catheter use rate†	xxxx/xxxx (xx.x%)	xxxx/xxxx (xx.x%)	x.xx (x.xx–x.xx)	x.xx
Urinary catheter use rate†	xxxx/xxxx (xx.x%)	xxxx/xxxx (xx.x%)	x.xx (x.xx–x.xx)	x.xx
Tidal volume > 8 mL/kg of predicted body weight†	xxxx/xxxx (xx.x%)	xxxx/xxxx (xx.x%)	x.xx (x.xx–x.xx)	x.xx
Tidal volume, mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx
Safety culture (SAQ score, by domain), mean difference (SD)				
Team work climate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx
Safety climate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx
Job satisfaction	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx
Stress recognition	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx
Perception of management	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx
Work conditions	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x–xx.x)	x.xx

RASS = Richmond Agitation–Sedation Scale. SAQ = safety attitudes questionnaire. * All estimates of effect are adjusted for baseline values of the outcome variable. † Odds ratio, patient-days delivered/total patient-days (%).

Figure 4. Multiple mediation model showing relationship between the independent variable (study intervention), mediators and the dependent variable (inhospital mortality)



a^i, b^i = mediator pathways. c^1 = effect pathway independent of mediators.

number of statistical tests, quantifies the effects of the mediation, and does not assume that the indirect effects are normally distributed. We will use the R package mediation with random effects models.[23,24]

Subgroup analysis and analysis of heterogeneity of treatment effect (HTE)

We analyse the effect of the intervention on the primary outcome according to the following subgroups: two strata of baseline inhospital mortality (by median) observed for ICUs in the preparatory observational phase; public v private hospital; medical v surgical patient; two strata of the SOFA score; presence of sepsis at admission; and need for MV at admission. We will explore how treatment effect varies by patient baseline risk of death (estimated by baseline SAPS 3) in a more detailed fashion. That is, we will assess treatment effect on inhospital mortality according to patient baseline SAPS 3, 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 preparatory observational phase. We will perform subgroup analysis irrespective of intervention efficacy. We will assess the statistical significance of subgroup effects by formal tests of interaction.

Sensitivity analysis

As a sensitivity analysis, we will assess the effect of the multifaceted intervention on primary outcome considering only ICUs which were adherent to the study protocol, ie, those that applied checklists and clinician prompting on at least weekdays ($\geqslant$ 72% of total patient-days).

We will carry out adjusted and unadjusted cluster-level analyses with beta-regression models for the primary outcome to check that conclusions are robust.[25]

We will present before-and-after within-group differences and 95% confidence intervals as supplementary material (Appendix Table 2) (see cicm.org.au/Resources/Publications/Journal). We will also calculate between-group differences in before-and-after differences using mixed-effects regression models with group–phase interaction terms to allow for possible before-and-after changes in the control group due to secular trends or the Hawthorne effect (Appendix Table 2).

Missing data

If there are losses to follow-up for the primary outcome data, we will attribute the data using multiple imputation techniques. Nevertheless, we expect minimal loss of primary outcome data. For all other outcomes, we will analyse only patients with complete data (complete case analysis).

Conclusion

We report our plan for analysing the data from the Checklist-ICU study before closing the study database and starting analysis. We believe that this document will enhance the utility of the reported results and allow readers to better appraise their impact.

Acknowledgements

The study is funded by ANVISA, the Brazilian Ministry of Health and the Brazilian Development and Social Bank, through the Program to Support Institutional Development of Universal Health System, in partnership with Hospital do Coração and Hospital Samaritano. The D'Or Institute for Research and Education also contributed funding

for the trial, and the Latin American Sepsis Institute provided support for the study. The funding sources have no role in the design, execution, analysis, or decision to publish the results.

Competing interests

None declared.

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Appendix Table 1. Baseline patients' characteristics determined in the observation preparatory phase and randomised phase

Characteristic	Intervention arm		Control arm	
	Baseline phase (x ICUs, x patients)	Randomised phase (x ICUs, x patients)	Baseline phase (x ICUs, x patients)	Randomised phase (x ICUs, x patients)
Patient level characteristics				
Age – yr – mean ±sd	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x
Female sex – no. (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Type of admission				
Medical – no. (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Elective surgery – no. (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Emergency surgery – no .(%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Reason for ICU admission				
Post-operative care	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Respiratory failure (except sepsis)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Shock (except sepsis)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Neurological	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Cardiovascular	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Gastrointestinal	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Haematological	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Other	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Comorbidities				
Cancer treatment, metastatic or haematological	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)

Cirrhosis	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
AIDS	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
SAPS 3 score at admission – mean ±sd	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x
SOFA score at admission – mean ±sd	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x

Appendix Table 2. Outcomes reflecting clinical events, processess of care and culture in the baseline preparatory and randomised phase and between group differences in pre-post differences

Variables	Intervention arm			Control arm			Between group difference in pre-post differences (95% CI)	P value
	Baseline phase (x ICUs, x patients)	Randomised phase (x ICUs, x patients)	P value	Baseline phase (x ICUs, x patients)	Randomised phase (x ICUs, x patients)	P value		
Primary outcome								
In-hospital mortality– no./total no. (%)*	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Secondary clinical outcomes								
ICU mortality – no./total no. (%)	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Catheter-related bloodstream infection – no./1000 patients-day	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Ventilator-Associated Pneumonia – no./1000 patients-day	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Urinary tract infection – no./1000 patients-day	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Ventilator-free days in a 28-day period – mean ±sd	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
ICU length of stay – mean ±sd	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Hospital length of stay – mean ±sd	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Processes of care								
Head of bed elevated ≥ 30°	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Adequate prophylaxis for venous thromboembolism	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Adequate sedation (RASS -3 a 0)	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Central venous catheter use rate	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Urinary catheter use rate	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Analgesic use rate	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Antibiotic use rate	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx
Tidal volume > 8 mL/kg of predicted body weight	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	xx/xx (xx.x)	xx/xx (xx.x)	x.xx	x.xx	x.xx

Tidal volume, mean ±sd	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Safety culture								
Safety Attitudes Questionnaire – score by domains								
Team work climate	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Safety climate	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Job satisfaction	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Stress recognition	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Perception of management	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx
Work conditions	xx.x±xx.x	xx.x±xx.x	x.xx	xx.x±xx.x	xx.x±xx.x	x.xx	x.xx	x.xx