Comparison of Tele-Critical Care Versus Usual Care On ICU Performance: The TELESCOPE trial

Statistical Analysis Plan

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SAP Version History

Version	Comment
Original SAP: Version 1.0 (September 2018)	same as protocol trial NA
Current SAP: Version 1.1 (October 2020, revised July 2021)	1 – Revision and re-estimation of the expected power accounting for information from the baseline period 2 – Clarification about the analysis population 3 – Specification of the core variables for multiple imputation if needed 4 – Specification of the model and co-variates for the main analysis 5 – Revision and expansion of the subgroups to be evaluated

Table of Contents

1. Background and rationale

Healthcare demand for critically ill patients admitted to Intensive Care Units (ICUs) has been expanding worldwide, causing a great social impact.[1] Brazil is sensitive to this issue as it experiences great regional disparities and population ageing without adequate control of the main health determinants.[2–4] This scenario justifies seeking efficient care for ICU patients.[5]

Daily multidisciplinary round (DMR) is an approach that optimizes the ICU care.[6–8] DMRs consists of systematic patient-centered discussions aiming to establish joint therapeutic goals for the next 24 hours of ICU care.[6] However, full implementation of DMR is still challenging.[6] Telemedicine in critically ill patients, known as tele-ICU, has gained relevance.[9] However, the benefit of tele-ICU lacks high quality scientific evidence, particularly outside high-income countries.[10,11] Furthermore, most of the studies published so far address Telemedicine in ICUs using vital signs monitoring and a continuous response system in a costly way.[12] Thus, little is known about the use of Telemedicine focused primarily on supporting DMR, which is understood to be both effective and more feasible from the economic perspective. The TELESCOPE trial aims to evaluate whether an intervention consisting of guided DMRs, supported by a remote specialist (intensivist) through Telemedicine and audit-feedback on care performance, will reduce ICU length of stay compared to a control group.

To prevent outcome reporting bias and data-driven analysis results, the International Conference on Harmonization of Good Clinical Practice (ICH-GCP) recommends that clinical trials should be analyzed according to a pre-specified detailed Statistical Analysis Plan (SAP). This document presents the updated and finalized SAP of TELESCOPE trial. Recruitment for

the trial has now been completed, but data collection is still running and no data analysis has yet been undertaken.

2. METHODS

2.1. Study design and setting

The TELESCOPE trial is a national, multi-center, controlled, open label, cluster-randomized trial. The study tests the effectiveness of daily multidisciplinary rounds conducted by an intensivist through Telemedicine in Brazilian ICUs. The protocol was approved by local Research Ethics Committee (IRB) of the coordinating study center (Hospital Israelita Albert Einstein) (CAAE: 01523118.0.1001.0071) and by the local IRB from each one of the 30 ICUs, following the Brazilian legislation.

2.2. Inclusion and exclusion criteria

2.2.1. Eligibility criteria for ICUs (clusters)

At the cluster level, ICUs of public or philanthropic hospitals, with a minimum of 8 ICU beds and with on-site registered doctors and nurses were eligible for inclusion.

We excluded ICUs that already presented DMRs, defined as:

1) Meetings (DMRs) ≥ 3 times per week, during weekdays, conducted by a certified intensivist and documented in medical records with fixed visit length (>5 min / patient), using some supporting tool (checklist or standard form), goal-oriented, based on established protocols, including all the patients admitted to the ICU

or

2) Monthly management of indicators (audit and feedback) with specific planning. We also excluded specialized ICUs (ICUs admitting exclusively cardiac surgery, neurological, burned patients) and step-down units or coronary units. Only one unit per hospital was allowed.

2.2.2. Inclusion criteria for patients

At the patient level, all consecutive patients admitted to the ICU, aged 18 years or older after the beginning of the trial.

2.2.3. Exclusion criteria for patients

We excluded patients admitted to the ICU due to justice-related issues (since in such circumstances the ICU admission or discharge may be determined by the law rather than by medical reasons) and patients previously included in the TELESCOPE trial (for the analysis of the primary outcome).

2.3. Intervention

Briefly, the trial intervention consists of DMR led by remote intensivists with the local multidisciplinary team (doctor, nurse and physiotherapist). DMRs take place from Monday to Friday, in predetermined hours (mostly during the mornings), using Telemedicine equipment, and they approach every patient admitted to the participating ICUs. Clinical protocols in texts and video formats (developed and used during the tele-intensivists training period) were made available to physicians and multidisciplinary team of the ICUs in

the intervention arm, right after randomization and establishment of a DMR routine. Tele-intensivists do not write medical prescriptions, nor do they give direct orders to the local care team for procedures or interventions. DMRs may be postponed, interrupted or suspended in case of urgency / medical emergency situations that may hinder participation of local doctors.

Additionally, ICU performance indicators are presented for each coordinator of the participating ICUs as well as for tele-intensivists, and monthly remote meetings between the local ICU team and the respective tele-intensivist are organized to discuss these indicators and to establish possible improvement action plans.

Control Group (usual care): no interventions are delivered to the ICUs randomized to the control group, except for the systematic data collection required for the comparisons described in the trial objectives. However, unlike in the ICUs of the intervention group, the ICU performance indicators originated from the collected data are not discussed with the care team or the coordination of the participating ICUs.

2.4. Randomization and masking

After a 2-month observation period (baseline period) in which performance indicators for eligible ICUs were collected without any intervention (with the purpose of obtaining data for randomization, analysis and characterization of the initial ICU status), the ICUs eligible for the study were randomized. The 30 ICUs were randomly assigned to either the intervention group (n=15) or the control group (n=15) using a restricted randomization algorithm that minimizes imbalance between treatment groups across the following baseline covariates at the ICU level:[13,14]

1) number of ICU beds

2) mean SAPS 3, in points
3) mean ICU length of stay (LOS), in days
4) Standardized mortality rate (SMR)
5) Standardized resource use (SRU), and
6) A two-category dummy indicator for Brazilian region where the ICU is located (regions South and Southeast x regions North/Northeast/Central-West).

We followed all the steps recommended by Carter and Hood during the application of the minimization algorithm.[13] The randomization was performed at three times, including 14 units during the first randomization, followed by 7 and 9 units (Figure 1). We decided a priori to randomize at three times and the number of units at each randomization was pragmatic, allowing for ethical approval and completion of the baseline period, respecting the minimum of eight units during first randomization and minimum of six on subsequent randomizations.[13]

For the first randomization, we followed the steps: 1) the database with the baseline data (2 months) were locked, 2) derivation of the six covariates per unit, 3) run the algorithm, generating the potential combinations of unit's allocation, 4) a random combination of allocations was selected. The order of each unit in the database was randomly sorted before the algorithm, as well as the order of potential allocations. The select allocation was coded as 0 and 1 by the algorithm. To select whether intervention would be 0 or 1, we performed the final simple randomization and 0 was allocated to the intervention arm. For the second and third blocks, we followed the same steps: we entered the baseline data of the previous block with its allocation and the new covariates. The algorithm accounts for the previous block covariates to calculate the new balance between

arms. We applied the same random sorting of order and potential unit allocations. The meaning of 0 and 1 was kept the same as the first block randomization (i.e., 0 to intervention and 1 to control) because it must follow the first block ascertainment.[13] To ensure allocation concealment, all units were enrolled prior to randomization and the Ethics approval and the ICU and hospital coordinators signed the agreement with commitment to the trial; the statistician responsible for the randomization list received only the ICU identifier code, unaware of which unit it referred to; the allocation list was sent to the study coordinator, who informed simultaneously the ICUs about the randomization and allocation.

The allocations were done after the completion of the baseline, on 05 August 2019, 16 October 2019, and 29 January 2020, using the software R (v. 3.5.2).

Figure 1. Time periods of 30 units in the TELESCOPE trial.

		2019							2020			...	2021
Randomization	Number of Units	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Fev	Mar	...	April
First	14	Baseline	Baseline	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	End enrolment*
Second	2	Waiting IRB	Baseline	Baseline	Interstitial	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	End enrolment*
	5	Waiting IRB	Waiting IRB	Baseline	Baseline	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	End enrolment*
Third	2	Waiting IRB	Waiting IRB	Waiting IRB	Baseline	Baseline	Interstitial	Interstitial	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	End enrolment*
	4	Waiting IRB	Waiting IRB	Waiting IRB	Waiting IRB	Baseline	Baseline	Interstitial	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	End enrolment*
	3	Waiting IRB	Waiting IRB	Waiting IRB	Waiting IRB	Waiting IRB	Baseline	Baseline	Intervention / Control	Intervention / Control	Intervention / Control	Intervention / Control	End enrolment*

* From April the data collection will continue until hospital outcome or 90-days post ICU admission. The intervention will be maintained in the whole unit until the last included patient is discharged from the ICU.
Interstitial was the period when the ICUs completed their baseline period of two months and were waiting for more blocks to complete their 2-month period to be randomized as a block.

The intervention is open due to the nature of the study (Tele-ICU rounds, quality improvement meetings and delivery of evidence-based clinical protocols). The steering and scientific committees are blinded to the DMRs and monthly feedback/audit meetings.

2.5. Outcomes

2.5.1. Primary outcome

At an individual level, the primary outcome of this trial is ICU length of stay, measured in days, taking into account the time interval in hours between patients' ICU admission and ICU discharge times (i.e., transfer to another care facility or another hospital) or ICU death, as defined by the hospital's system date and time. Date and time will be entered by the health care worker responsible for data collection. ICU LOS will be derived in 24h periods with decimal places, as recommended.[15]

2.5.2. Secondary exploratory outcomes

The secondary outcomes of this study include assessing the impact of interventions implemented through Telemedicine compared with a control group in the following outcomes:

At the unit level:

- Classification of the unit according to the profiles defined by the SRU and the SMR.[16,17] The SRU reflects the observed / expected rate of resources used (estimated as ICU length of stay for surviving patients), adjusted by the patient's severity of illness (SAPS 3).[18]

  The SMR reflects the observed / expected rate (according to severity score) of hospital deaths. The profiles are a combination of SMR (above or below median) and SRU (above or below median): Each unit can be assigned to one of the four groups:

"most efficient" (SMR and SRU < median); "least efficient" (SMR, SRU > median); "overachieving" (low SMR, high SRU), "underachieving" (high SMR, low SRU).[17]

At an individual level:

- In-hospital mortality, defined as death by any cause, within the period from the date of ICU admission to the date of hospital discharge or death, whichever comes first.
- Incidence of central line-associated bloodstream infection (CLABSI), as defined by the CDC.[19]
- Incidence of ventilator-associated event (VAE), as defined by the CDC.[20]
- Incidence of catheter-associated urinary tract infection (CAUTI), as defined by the CDC.[21]
- Ventilator-free days at 28 days, defined as the number of days from successfully weaning to day 28; patients who died before weaning were deemed to have no ventilator-free days
- Rate of patients receiving oral or enteral feeding, defined as any amount of oral or enteral diet, during ICU stay
- Rate of patients under light sedation or alert and calm [Richmond Agitation-Sedation Scale (RASS) = -3 to +1]
- Rate of patients under normoxemia [peripheral oxygen saturation (SpO_2) between 92% and 96%]

2.5.3. Other exploratory outcomes

Other outcomes, considered merely exploratory, will be observed:

- ICU mortality

- 24-hour ICU readmission rate
- Proportion of mechanical ventilation (MV) use
- Early reintubation rate (<48h after extubation)
- Accidental extubation rate
- Rate of patients with head of bed elevation for patient under MV
- Rate of central venous catheter (CVC) use and duration
- Rate of urinary catheter use and duration
- Rate of adequate prevention of venous thromboembolism (VTE)
- Rate of patients with adequate glycemic control

The follow-up time to define all outcomes will be truncated at 90 days from ICU admission.

2.6. Power calculation

2.6.1. Original power calculation

Prior to the start of the trial and baseline period, for the funding application, we estimated a mean ICU length-of-stay of 8 [standard deviation (SD) 10] days for general adult public ICUs in Brazil. We used data from published literature and reports from the online project "UTIs Brasileiras".[22] In 2018, the "UTIs Brasileiras" dashboard had data of ICU LOS from 242 public ICUs in Brazil (n=3,199 beds). Using data from 20 ICUs (10 ICUs from Ranzani et al,[23] 10 ICUs from the ORCHESTRA study,[24] available in the *ems* R package), we estimated an intraclass correlation coefficient (ICC) of 0.018. Considering a two-arm cluster trial with an ICC of 0.018, for a minimum difference of an average length of stay of 1.5 days (8.0 to 6.5 days)

and SD of 10 days, power 80%, alpha 5%, we would need a total of 30 clusters (15 intervention units and 15 control units) with an average cluster size of 500 patients per ICU over a period of 18 months. Cluster size can vary and if the cluster size variation is high, usually measured by the coefficient of variation (CV), the power of the trial decreases. We estimated the CV using the expected minimum and maximum method of the cluster size:[25] assuming a minimum cluster size of 350 patients and maximum of 650 patients (i.e., range 300, approximated SD of 75), for a mean size of 500 patients, we would have an approximated CV of 0.15 and maintain 80% power.

2.6.2. Power after baseline period

We had pre-specified in the original protocol that once the baseline period was completed, we could review the power calculation. We evaluated the baseline period and the mean ICU LOS was 7.8 days, SD 9.8 and an ICC of 0.087 for a model without covariate adjustment. We had an ICU LOS mean and SD very close to the original power calculation (mean 8 and SD 10), but higher ICC than predicted. The original power estimation did not account for the use of the data from the baseline period in the model for the primary outcome, because it was not certain we would have funding to collect individual-level data for the selected ICUs to characterize the baseline period. However, we specified in the original protocol that once the baseline period was established, we would adjust the model for the primary outcome accounting for the baseline period and re-estimating the power of the trial. Therefore, using the framework suggested by Hemming et al,[26] we re-estimated the power accounting for the baseline period in September 2019. This method uses the cluster auto-correlation (CAC), defined by the ratio of the between-period ICC to the within-

period ICC. Considering a cluster parallel trial with baseline measure, with cross-sectional sampling structure, a correlation structure of a two-period decay, a coefficient of variation of clusters size of 0.4 (taken from the baseline period), we would maintain 80% power until a CAC value of ≥0.906, without considering covariate-adjustment. We estimated the CAC on the 20 ICUs used for the estimation of initial ICC, using follow-up periods similar to the TELESCOPE trial, and in all occasions it was higher than 0.960. Considering the dynamic of ICU LOS and its high correlation overtime, we expect CAC to be high. Two issues that could reduce the power must be taken into account: 1) this new power calculation assumes that ICUs would have the same number of patients recruited in the baseline and post-randomization period (n=500); 2) equal number of ICUs randomized to intervention and control at each block, which occurred in the first block, but not for the second and third block. However, these estimations did not account for the covariate adjustment in the main model, also pre-specified in the original protocol, which decrease the ICC and increase precision by reducing the between-center variance and that we will adjust for randomization block in the analysis. Based on this scenario, after a meeting with an external advisory board on 05/10/2020, the steering committee decided to keep the original sample size and power calculation, conditioning it to updating the analysis plan in order to keep the covariate adjustment and to account for the baseline period.

3. Data collection and management

A detailed description of data collection and management is described in the protocol paper.[27] Data collection procedures will be identical in the ICUs assigned to control and to intervention arms, following 1) At ICU admission, including date and hour of admission,

demographic variables, SAPS 3 and SOFA score, reason for admission, comorbidities, functional status, organ support, among others; 2) Data regarding data to ascertain secondary and tertiary outcomes will be collected daily, including documented treatment goals from the DMR; 3) Upon ICU discharge, data on date and time of ICU discharge, place of discharge, and outcome; 4) And finally, at hospital discharge, date and time and outcome.

Trained health care workers collected data, without any involvement of the study committees and investigators. We developed standard CRFs for the trial, with extensive validation and piloting aiming to achieve clarity and consistency. Data was imputed using electronic CRFs in the Research Electronic Data Capture system (REDCap®, USA) via Internet and hosted on a server at the Hospital Israelita Albert Einstein/São Paulo - Brazil.

Data from the intervention arm regarding adherence to the intervention was collected. The main indicators for adherence to the intervention were defined as:

a. DMR rate per site/bed/day and DMR duration (including individual and periodic feedback to each tele-intensivist).

b. Rate of recommendations made and validated (accepted and not accepted)/DMR.

c. Monthly meeting on performance indicators reports: tele-intensivists will send monthly reports to study team, including the executive summary (file sent to the leaderships of each study center/intervention arm, before the monthly meeting) and the meeting record file (structured data about highlighted indicators, action plan, responsibility, and due dates).

d. Access to the clinical protocols: absolute number of accesses to the video-protocols will be provided and followed.

4. Statistical methods analysis

4.1. General analysis issues

4.1.1. Analysis population

Primary statistical analyses will be performed according to the intention-to-treat principle. Patient outcomes will be analyzed according to the randomization of the ICU each patient was in, regardless of whether or not the intervention was applied in that ICU. The baseline period is defined as the first two months of data collection in each ICU. The period for the evaluation of the intervention will be defined as the day after the randomization, thus patients admitted to the ICUs the next day of randomization are accounted as of the intervention/control period. Primary statistical analysis will also consider the baseline period in the analyses, while patients admitted to some of the ICUs during the "Interstitial" period (between baseline and randomization) will be excluded.

4.1.2. Database locking

All analyses planned in this statistical analysis plan will be conducted only after the database locking. The data management and checks for missing and consistency will be conducted blinded to the ICU code and allocation.

4.1.3. Missing data

We will perform multiple imputation if missing data on core variables is >5%, under the assumption that the missingness pattern is missing at random (MAR) conditional on the observed data.[28] Core variables are defined as the covariates to be used in the main analysis of the primary outcome: SAPS-3 score, type of ICU admission, invasive mechanical

ventilation at ICU admission, number of ICU beds in the baseline, Brazilian region where the ICU is located, ICU performance in the baseline and order of randomization. We will follow the recommended and standard steps for multiple imputation.[28] We will include the outcome and account for the clustered structure of the data. The imputation model will have the covariates used in the main model and auxiliary variables. We will start with 20 imputed datasets and change the number of imputed datasets based on the fraction of missing information (MFI).[29] We will pool the estimates using Rubin's rules. The random number seed will be set to 2605.

For the severity scores, SAPS 3 and SOFA, we will consider "zero points" or "normal values" where data are missing. In case we perform multiple imputation, we will impute the final composite score.

4.1.4. Multiplicity

Pre-specified secondary outcomes and subgroup analyses will not be adjusted for multiple comparisons. They should, therefore, be interpreted as exploratory.

4.1.5. Other issues

We will not compare baseline characteristics between treatment groups with Null hypothesis significance testing (NHST).

We will evaluate the calibration for in-hospital mortality of the SAPS3 score with data from the baseline period. If necessary, we will recalibrate the model for the studied population. All analyses will be performed with program R (3.4.1 version, the version will be updated at the time of analysis).

The TELESCOPE trial has been running during the COVID-19 pandemic. It is likely that the pandemic changed the usual characteristics of the admitted patients, both if an ICU from the TELESCOPE trial becomes a reference for COVID-19 patients or for non-COVID-19 patients. The ICU performance, both at control and intervention arms, could have influenced the decision-makers at the Federal, State and Municipal level to decide on referring an ICU to be COVID-19 or not. As ICU performance is, in this case, post-randomization, we will not adjust for whether an ICU is reference for COVID-19 or not in the analysis, otherwise it will break the randomization. Neither the steering committee nor tele-intensivists were responsible for any decision about an ICU being a reference or not to COVID-19.

4.2. Statistical analyses

We will follow the framework proposed in the literature to optimize the power and properly account for time in cluster parallel randomized trials with baseline period (longitudinal cross-sectional cluster trials).[26,30,31] Thus, we will consider the baseline individual data allowing the secular trend to vary randomly across clusters by extending the random-effects components with an interaction between cluster and time period (baseline vs after randomization).[30] This term also allows for the ICC to differ from observations that are made in the same or different time periods and for estimating two ICCs (the "within-period ICC" and the "between-period ICC") used to estimate the CAC (the ratio of the between-period and within-period ICCs).

4.2.1. Analysis of the primary outcome

The linear mixed model for the primary outcome will be the following:

$$Y_{ijk} = \beta_0 + \beta_1 X_{ij} + \beta_2 j + \beta_3 Z_{ijk} + \beta_4 L_{ij} + \mu_i + \nu_{ij} + \epsilon_{ijk} \quad \text{Equation (1)}$$

for cluster *i*, time-period *j* and participant *k*, where X_i denotes the trial arm for cluster *i* (coded 0 or 1), and *j* denotes the time-period in which participant *k* in cluster *i* is assessed (0 for baseline, 1 for after randomization). The individual error term is assumed to be Normally distributed and independent of ν_{ij} and μ_i. Random terms are assumed to be Normally distributed, and ν_{ij} is assumed independent of μ_i. Z_{ijk} and L_{ij} are the matrix of covariates at the individual level and unit level, respectively. β_1 is the coefficient of interest for the trial, i.e., the estimate for the difference between those receiving the intervention and those in the control group.

For the primary outcome, we will include the index admission of a patient, i.e., we will not include ICU readmissions. The primary outcome – ICU LOS – will be log-transformed to account for the normality of the residuals of the linear mixed model. These two steps (not including readmissions and log-transformation) were used for the power calculations.

We will use the identity link in the model for the primary outcome and the Satterthwaite's degree-of-freedom correction.[14,32,33]

4.2.2. Per protocol analysis for the primary outcome

We are planning a sub-study to evaluate a per-protocol analysis in the TELESCOPE trial. We will use the principles of causal inference and deal with post-randomization

confounding and biases, keeping the inference based on the randomization.[34] We plan to use the principal stratification approach.[35]

4.2.3. Sensitivity analyses for the primary outcome

These two sensitivity analyses regarding the primary outcome were pre-specified in the original protocol.

4.2.3.1.Readiness for discharge

The primary outcome – ICU LOS – is an outcome that depends also on factors outside the ICU for those that improved during the ICU stay, such as ward bed availability.[36] For this reason, we specified to also measure the ICU LOS in terms of readiness for discharge, i.e., days from ICU admission to the first day the attending team defined the patient was ready to be discharged alive. This variable was measured during the daily collection data and will be measured as counts, because we will not have time accuracy for its measurement. The attending clinicians were not aware that this would be an outcome of the TELESCOPE trial. We will fit the Equation (1) using generalized linear mixed models to accommodate it using a Poisson or negative-binomial family with a log link.

4.2.3.2.Competing risk of death

The primary outcome – ICU LOS – is subject to the competing risk of death.[15] Therefore, the ICU LOS represents a composite summary of two process: time to ICU discharge alive and time to ICU death. There are alternatives to deal with this scenario, such as 1) fitting competing risk models, modeling time to discharge alive and consider time to ICU death as a competing event, 2) analyzing LOS separately between ICU survivors and

non-survivors, 3) weighting differently the LOS for those who died, among others. As expected, the potential different results on the primary outcome analysis will likely occur or be relevant only if the intervention has an effect on mortality. We consider this a secondary analysis because, a priori, we did not expect a major impact of the intervention on mortality. In this sensitivity analysis, we will use the competing risk framework, presenting the analysis with cause-specific hazard ratios and sub-distribution hazard ratios for the time to discharge alive.[37] The models will be adjusted for the same six covariates as the primary analysis, and the baseline period will be accounted as the mean ICU LOS at the unit level in the baseline period. We will account for the correlated data structure with a "shared frailty model".

4.2.4. Analysis of secondary outcomes at ICU level

The main outcome at the ICU level is the ICU performance classification. The performance will be defined in the baseline and after intervention periods without considering if the unit is in the intervention or control group. Thus, we will estimate if there will be a shift towards better performance for the ICUs in the intervention group, i.e., if there will be more commonly "most efficient" and "overachieving" ICUs in the intervention group.

Based on the background that the intervention might be more efficient overtime, in an exploratory analysis we will analyze the ICU performance classification at the last 3 months of the intervention.

For the ICU level outcomes, we will include all patients who fulfilled all inclusion criteria and none exclusion criteria, and we will include readmissions.

4.2.5. Analyses of secondary outcomes at patient level

For all secondary outcomes at the individual level, we will fit the Equation (1) using generalized linear mixed models to accommodate each secondary outcome (e.g., logistic mixed model for mortality; Poisson/negative-binomial for rates, etc.). We will adjust for the same covariates, except when it is not possible because of the outcome type. For instance, ventilator associated events can be measured only in patients with invasive mechanical ventilation.

For the secondary outcomes that involve rates or patient-days, catheter-days and etc., we will include all patients who fulfilled all inclusion criteria and none exclusion criteria, and we will include readmissions.

4.2.6. Covariate adjustment

We pre-specified that the analyses for the primary and secondary outcomes will be adjusted by covariates in the original protocol, but we did not define which covariates, except the mean ICU LOS at the cluster level. Based on the literature on the determinants of ICU LOS, we will adjust by three patient level covariates and four ICU level covariates:

1) SAPS-3 (continuous term),

2) Type of ICU admission (3 categories: medical, elective surgical, unplanned surgical),

3) Invasive mechanical ventilation at ICU admission (2 categories: yes, no),

4) Number of ICU beds in the baseline (continuous term),

5) Brazilian region where the ICU is located (2 categories: South/Southeast, North/Northeast/Central-West),

6) ICU performance in the baseline (4 categories: most efficient, least efficient, overachieving, underachieving).

7) Groups of randomization (3 categories: first, second and third blocks)

4.2.7. Subgroup analysis for the primary outcome

We pre-specified in the original protocol three subgroups, as follows:

1) Type of admission (medical vs. surgical),
2) Tertiles of SAPS3 and
3) Mechanical ventilation status (invasive MV vs. not-invasive MV).

We now revised their definition for clarification and added three additional subgroups, based on the main research question of the trial and the literature. Thus, the final six subgroups are defined below:

1) Type of ICU admission (3 categories: medical, elective surgical, unplanned surgical)
2) Tertiles of SAPS 3 score (defined by “ntile(SAPS3,3)”)
3) Invasive mechanical ventilation at ICU admission (2 categories: yes, receive invasive mechanical ventilation at ICU admission; no, receive other respiratory support rather than invasive mechanical ventilation or none)
4) Age groups (3 categories: 18-39 years, 40-59 years, 60+ years)

5) ICU performance in the baseline (4 categories: most efficient, least efficient, overachieving, underachieving)
6) Calendar time from the intervention in trimesters (as categorical)

Sub-groups will be analyzed adding an interaction term between the X_{ij} in Equation (1) and the subgroup of interest, and a term for the fixed effect of the subgroup of interest if it is not already a covariate. The p-value for the interaction will be evaluated by a likelihood ratio test comparing the model without the interaction and with the interaction.

5. Reporting

We will follow the CONSORT extension for cluster-randomized trials.[38] The results of the TELESCOPE trial will be reported transparently, regardless of its results, and disseminated to the participating centers, funding agency, scientific community, and community. Any deviation from the protocol and this SAP will be highlighted.

5.1. Proposed Figures and Tables

5.1.1. CONSORT flowchart

We will present the screening and recruitment as the CONSORT diagram from the extension for cluster-randomized trials.

5.1.2. Table of intensive care unit characteristics by treatment groups

	Baseline period	
	Intervention	**Usual care**
Number of ICUs	N	N
Cluster size	mean ± SD	mean ± SD
ICU beds (mean ± SD)	mean ± SD	mean ± SD
SAPS 3 (mean ± SD)	mean ± SD	mean ± SD
ICU LOS (mean ± SD)	mean ± SD	mean ± SD
SMR (mean ± SD)	mean ± SD	mean ± SD
SRU (mean ± SD)	mean ± SD	mean ± SD
Region	N (%)	N (%)
Type: public / philanthropic	N (%)	N (%)

5.1.3. Table for patient level characteristics by period and treatment group

	Baseline period		**Intervention period**	
	Intervention	**Usual care**	**Intervention**	**Usual care**
Number of patients	N	N	N	N
Age, years	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Female sex	N (%)	N (%)	N (%)	N (%)
Comorbidities	N (%)	N (%)	N (%)	N (%)
Performance status	N (%)	N (%)	N (%)	N (%)
Pre ICU LOS, days	mean ± SD	mean ± SD	mean ± SD	mean ± SD
	median [p25-p75]	median [p25-p75]	median [p25-p75]	median [p25-p75]
Type of admission	N (%)	N (%)	N (%)	N (%)
Reason for ICU admission	N (%)	N (%)	N (%)	N (%)
SAPS 3, points	mean ± SD	mean ± SD	mean ± SD	mean ± SD
SOFA score, points	mean ± SD	mean ± SD	mean ± SD	mean ± SD
	median [p25-p75]	median [p25-p75]	median [p25-p75]	median [p25-p75]
Number of organ dysfunctions	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Advanced organ support at ICU admission				
Non-invasive mechanical ventilation	N (%)	N (%)	N (%)	N (%)
Invasive Mechanical ventilation	N (%)	N (%)	N (%)	N (%)
Vasoactive drugs	N (%)	N (%)	N (%)	N (%)

5.1.4. Table with the effect estimates of the intervention

	Intervention ICUS		Control ICUs				
	Baseline period	Intervention period	Baseline period	Intervention period	Effect estimate type	Adjusted Effect estimate (95% CI)	P Value
Primary outcome							
Number of patients	N	N	N	N			
ICU LOS, days	mean (SD)	mean (SD)	mean (SD)	mean (SD)	AAA	X.XX (X.XX to X.XX)	0.XXX
Sensitivity analyses of primary outcome definition							
Readiness for discharge	mean (SD)	mean (SD)	mean (SD)	mean (SD)	AAA	X.XX (X.XX to X.XX)	0.XXX
Sensitivity analysis for the competing risk of death					AAA	X.XX (X.XX to X.XX)	0.XXX
Secondary outcomes							
Number of patients	N	N	N	N	AAA	X.XX (X.XX to X.XX)	0.XXX
Secondary Outcome Y	Z	Z	Z	Z	AAA	X.XX (X.XX to X.XX)	0.XXX
…	…	…	…	…	…	…	…

5.1.5. Forest plot with the subgroup analysis for the primary outcome

We will present a forest plot with the subgroup analysis for the primary outcome and embedded numbers, and the p-value for the interaction.

5.1.6. Times series of ICU LOS, SMR and SRU

We will present times series of ICU LOS, SMR, and SRU from baseline, aggregating the 2 months, and then aggregating every 3 months for the treatment and control group. In a supplementary figure, we will replicate it for each ICU.

We will present an alluvial plot with all 30 ICUs ICU performance categorized in 4 categories, with the time axis as of the times series.

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