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TITLE PAGE:

TELE-critical care verSus usual Care On ICU PErformance (TELESCOPE): protocol for a cluster-randomised clinical trial on adult general ICUs in Brazil

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ABSTRACT (word count: 298/300**)**

Introduction – The number of patients requiring admission to Intensive Care Units (ICUs) is increasing worldwide. Brazil is a developing country which suffers from consequences of demographic and epidemiological transitions in a scenario of great regional disparities and shortage of intensive care specialised physicians.

Methods and analysis - A multicentre, controlled, cluster-randomised superiority trial including 30 ICUs in Brazil (15 intervention and 15 control), from August 2019 to December 2020. In a parallel assignment, ICUs are randomised to a complex-intervention composed by daily rounds carried out through Tele-ICU by a remote ICU physician; development of local quality indicators dashboards coupled with monthly meetings with local leadership; and dissemination of evidence-based clinical protocols *versus* usual care. Primary outcome is ICU length of stay. Secondary outcomes include classification of the unit according to the profiles defined by the standardized resource use and the standardized mortality rate, hospital mortality, incidence of healthcare-associated infections, ventilator-free days at 28 days, patient-days receiving oral or enteral feeding, patient-days under light sedation or alert and calm, rate of patients under normoxaemia. All adult patients admitted after the beginning of the study in each participant ICU will be enrolled. Inclusion criteria (clusters): public Brazilian ICUs with a minimum of 8 ICU beds interested/committed to participating in the study. Exclusion criteria (clusters): units with fully established daily multidisciplinary rounds by an intensivist, specialized units (e.g., ICUs admitting exclusively cardiac surgical) or step-down units.

Ethics and dissemination - The study protocol was approved by the IRB of the Hospital Israelita Albert Einstein (coordinator centre), and by IRBs of each enrolled hospital/ICU. Statistical Analysis Protocol is being prepared for submission before the end of patient's enrolment. Results will be disseminated through conferences, peer-reviewed journals and to each participating unit.

Trial registration number - NCT03920501

Keywords: Telemedicine, Tele-ICU, Quality Improvement, Intensive Care.

ARTICLE SUMMARY:

Strengths and limitations of this study (Up to five short bullet points, no longer than one sentence each, that relate specifically to the methods)

- TELESCOPE is the first, large, multicentre cluster randomised trial performed in a middle-income country evaluating if a complex-intervention delivered mainly by TELE-ICU physician and aiming to optimize the care of critically ill patients impacts clinical outcomes.
- TELESCOPE trained general board-certified ICU physicians to deliver TELE-ICU consultancy and provide performance feedback to the attending team and managers, aiming a scalable intervention.
- TELESCOPE used a baseline period as reference for randomisation, by using a minimization algorithm in order to achieve balance between arms and decrease within cluster variability.
- TELESCOPE intervention occurs only inside the ICU and an expected limitation is that length-of-stay depends on factors outside the ICU, such as ward bed availability,

INTRODUCTION

Healthcare demand for critically ill patients admitted to Intensive Care Units (ICUs) has been expanding worldwide, causing great social impact.[1-3] Several factors have contributed to it, such as population ageing,[4] a higher prevalence of chronic diseases, among others.[3 5] Brazil is especially sensitive to this issue as it experiences great regional disparities and population ageing without adequate control of the main health determinants.[6-9] Such situation has resulted in a large number of frail elderly, who often require critical care due to acute aggravations in chronic conditions.[10-12] This scenario combined with the risk of spending a significant amount of money with suboptimal return for the society, justifies seeking efficient care for severely ill patients.[13]

Daily multidisciplinary round (DMR) is an approach that optimizes the ICU care. DMRs consists of systematic patient-centred discussions aiming to establish joint therapeutic goals for the next 24 hours of ICU care.[14] In different studies, DMR has been associated to better clinical outcomes.[15 16] However, full implementation of DMR is still challenging, since DMR must contain several attributes in order to maximize its results: its multidisciplinary character; proper settings; time and team standardizations; definition of roles; use of guiding tools; reduction of interruptions and focus on documented objectives.[14]

Telecommunication use for health care practice has been described since the advent of telecommunication.[17] The availability of high-speed data traffic has expanded the boundaries of Telemedicine, allowing the emergence of the first trial with critically ill patients in 1977.[18] In recent years, the use of Telemedicine in critically ill patients, known as tele-ICU, has gained relevance.[19] Specifically in the US, the number of ICU beds with some form of Telemedicine coverage has reached at least 15%.[20 21] There is a variety of possible tele-ICU applications, such as second opinion consultations in specific cases, monitoring of vital signs,

real-time performance and DMR conducted by a remotely located medical specialist.[22 23] . However, the benefit of tele-ICU lacks high quality scientific evidence, particularly outside high-income countries.[24 25] 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.[26] 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.

METHODS AND ANALYSIS

Aim and objectives

The TELESCOPE trial aims to answer to the following research question: Does a complex intervention offered by tele-ICU, focused on DMR attended by remote intensivists, improve ICU efficiency of adult general units in Brazil?

Primary Goal

- *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.

Secondary goals

- *To* evaluate whether an intervention consisting of guided DMRs, supported by a remote specialist (intensivist) through Telemedicine and audit / feedback on care performance improves indicators of ICU performance compared to a control group.

Study design and setting

The TELESCOPE trial is a national, multi-centre, controlled, open label, cluster randomised trial. The study tests the effectiveness of daily multidisciplinary rounds conducted by an intensivist through Telemedicine in Brazilian ICUs. Approximately 15,000 patients are expected to be recruited for a period of 18 months in 30 Brazilian ICUs (Figure 1).

After a 2-month observation period (baseline period) in which performance indicators for eligible ICUs is collected without any intervention (with the purpose of obtaining data for randomisation and characterization of the initial ICU status), the ICUs eligible for the study are randomised to either receive DMRs conducted by an intensivist through Telemedicine, from Monday to Friday, in addition to a monthly discussion of care performance indicators performed through virtual meetings (Intervention Group), or receive the unit's usual care (Control Group) (Figure 2). ICU board certified physicians receives a multicomponent training before starting the TELE-ICU DMR, comprising empathy and communication and quality improvement (Figure 3). The study protocol was registered in the Clinicaltrials.Gov (NCT03920501). The study protocol follows the recommendations of the SPIRIT 2013 Statement.[27]

Intervention

Intervention group (Tele-UTI) (Table 1)

Trial intervention consists of:

1. *Daily multidisciplinary rounds* (DMR) *led by remote intensivists*. Discussions are conducted by an intensivist located in a remote centre (tele-intensivist) and the local multidisciplinary team (doctor, nurse and physiotherapist). DMRs takes place from

Monday to Friday, in predetermined hours (mostly during the mornings), using Telemedicine equipment, and approach every patient admitted to the participating ICUs. The main objective of DMR conducted by a tele-intensivist is to discuss diagnostic hypotheses, active problems and create a treatment plan until the next DMR. Tele-intensivists make recommendations based on updated scientific evidence, suitable to the local context. Clinical protocols in texts and videos 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 randomisation and establishment of a DMR routine. Electronic forms for patient follow-up serves as a guideline (Index) and are filled out by tele-intensivists. According to the current regulation (national resolution from the Brazilian Federal Council of Medicine, CFM Resolution 1643 of 2002), tele-intensivists does not act directly upon patients, but are rather mediated by the local team. Therefore, the local healthcare practitioners implement the treatment plan. Indicators of adherence to recommendations made by tele-intensivists are registered. Tele-intensivists do not write medical prescriptions, nor gives 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.

2. *Management of ICU performance indicators.* The variables collected for the trial (table 1) are presented aggregately in reports available for each coordinator of the participating ICUs as well as for tele-intensivists. Data from Case Report Forms - CRFs (REDCap®, Vanderbilt University Medical Center, TN, USA) are used to automatically

feed dashboards in real-time, specially developed for this purpose (R Studio/Shiny®, Boston, MA, USA). In addition, 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 randomised to the control group, with the exception of the systematic data collection required for the comparisons described in the trial objectives. However, unlike in the ICUs of the intervention group, these indicators are not available for the care team nor to the coordination of the participating ICUs.

Sites

The list of potential units was retrieved from the national registry of health facilities ("Cadastro Nacional de Estabelecimentos de Saúde – CNES", in Portuguese), filtering those facilities with at least 8 ICU adult beds available.

Inclusion/Exclusion

The ICUs are invited by electronic means for an interview in which the eligibility and feasibility criteria below will be verified.

Inclusion criteria for ICUs

- ICUs of public or philanthropic hospitals
- ICUs with a minimum of 8 ICU beds
- ICUs with on-site doctors and nurses

Exclusion criteria for ICUs

- ICUs that already presented DMRs, defined as:

  - 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

  - Monthly management of indicators (audit and feedback) with specific planning.

- Specialized ICUs (ICUs admitting exclusively cardiac surgery, neurological, burned patients).
- Step-down units or coronary units

Patients

All consecutive patients that fulfil the inclusion criteria and none of the exclusion criteria will be enrolled.

Inclusion/Exclusion

The patients admitted in the ICU who currently meet the following inclusion criteria are included:

- Age ≥18 years old
- Patients admitted to the ICU after the beginning of the trial

Exclusion criteria for patients

- Patients admitted to the ICU due to justice-related issues (since in such circumstances the ICU admission or discharge may be determined by law and not medical reasons)
- Patients previously included in the TELESCOPE trial (for the analysis of the primary outcome).

Randomisation

The 30 ICUs are randomly assigned to either the intervention group (n=15) or the control group (n=15) using a restricted randomisation approach to ensure balance across the groups.[28 29] The randomisation unit will be the ICU to avoid contamination of the intervention. Only one ICU per hospital will be included in the trial. The randomisation is performed in blocks, sizes of 14, 7 and 9, following the completion of the baseline period. To ensure allocation concealment, the statistician responsible for the randomisation list receives only the ICU identifier code, being unaware of which unit it refers to. The allocation list is sent to the study coordinator, who informs the ICUs about the randomisation. The allocation will be maintained until the end of the study.

Blinding

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 of the DMRs and monthly feedback/audit meetings.

Follow-up

Patients are followed up until hospital discharge by the health care worker responsible for data collection.

Outcomes

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 time of transfer to another care facility or another hospital, 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.

Secondary exploratory outcomes

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

- Classification of the unit according to the profiles defined by the standardized resource use (SRU) and the standardized mortality rate (SMR).[30] The SRU reflects the observed / expected rate of resources used (estimated as ICU length of stay for surviving patients), adjusted by patient's severity of illness.[31 32] 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 four groups: "most efficient" (SMR and SRU < median); "least efficient" (SMR, SRU > median); "overachieving" (low SMR, high SRU), "underachieving" (high SMR, low SRU)[31]

- In-hospital mortality, defined as death by any cause from date of ICU admission until the date of hospital discharge or death, whichever comes first
- Incidence of central line-associated bloodstream infection (CLABSI), as defined by the CDC[33]
- Incidence of ventilator-associated event (VAE), as defined by the CDC[34]
- Incidence of catheter-associated urinary tract infection (CAUTI), as defined by the CDC[35]
- 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
- Patient-days receiving oral or enteral feeding, defined as any amount oral or enteral diet
- Patient-days under light sedation or alert and calm [Richmond Agitation-Sedation Scale (RASS) = -3 to +1]
- Rate of patients under normoxaemia [peripheral oxygen saturation (SpO_2) between 92% and 96%]

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

- Compliance to head of bed elevation for patient under MV
- Rate of central venous catheter (CVC) use and duration
- Rate of urinary catheter use and duration
- Adequate prevention of venous thromboembolism (VTE)
- Rate of patients with adequate glycaemic control

Data collection

At the patient level, the following data is collected (Table 2):

At the time of ICU admission:

- Identifier, date of birth, gender, main reason of ICU admission (adapted from APACHE III),[36] readmission status
- Anthropometric characteristics, comorbidities (adapted from SAPS3),[37] functional status (adapted from ECOG)[37]
- Respiratory, cardiovascular, and renal support
- Diet and sedation status
- Presence of devices: central venous catheter, arterial line, permanent catheters, urinary catheter, oro/naso-tracheal catheter and traqueostomy
- Date and time of hospital admission
- Date and time of ICU admission
- Simplified Acute Physiology (SAPS 3) score[32]
- Sequential organ failure assessment (SOFA) score[38 39]

Throughout the ICU admission:

- Documented goals from the DMR
- Documented discharge order status, defined as any mention to readiness to discharge or ICU transference order
- MV status and mechanical ventilation parameters
- SpO_2 range for patients on oxygen therapy
- Head of bed elevation for patients under MV
- Spontaneous respiratory test, accidental extubation or re-intubation events
- Need of vasoactive drugs and renal replacement therapy
- Continuous sedative infusion and light sedation strategy (reduction/daily interruption)
- Daily value (categorized below, above or within -3 to +1 range) of the RASS for patients undergoing continuous sedation at a predetermined time
- Adequacy of VTE prophylaxis
- Presence of oral or enteral nutrition
- Glycaemic control
- Notification of health-care-related infection episodes according to CDC (Centers for Disease Control and Prevention) criteria:
    - Central-line associated bloodstream infection (CLABSI)[33]
    - Ventilator-associated events (VAE)[34]
    - Catheter-associated urinary tract infection (CAUTI)[35]
    - Date and time of central venous catheter (CVC) insertion for patients undergoing CVC insertion
- Date and time of withdrawal of CVC for patients undergoing CVC insertion

- Date and time of indwelling urinary catheter (IUC) insertion for patients submitted to IUC insertion
- Date and time of withdrawal of IUC for patients undergoing IUC insertion
- Documentation of decisions for limiting the life support considering any mention to withholding or withdrawing in the medical records

At the time of ICU discharge

- Date and time of ICU discharge
- ICU outcome: discharge to ward, hospital transfer, death

At the time of hospital discharge

- Date and time of hospital discharge
- Hospital outcome: hospital transfer, death

Data collection and management

Trained health care workers collect data, without any involvement from the study committees and investigators. We developed a standard CRFs for the trial, with extensive validation and piloting aiming clarity and consistency.

Data is input 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. Medical data from tele-intensivist consultations is generated and stored using a specific platform developed by the Tele-ICU Department of the Hospital Israelita Albert Einstein/São Paulo - Brazil. Images and audio are never saved or stored. The

electronic files are stored in the hospital's servers in a controlled and secure environment to guarantee confidentiality. Furthermore, access to all documents is user and password controlled. To ensure data quality, the following procedures are performed:

- All professionals responsible for data collection are trained before the beginning of the trial in order to guarantee clear definitions for accurate data collection;
- A research nurse from the Coordinating Centre is available 24/7 to solve any problem and question about data collection;
- Data input in the system are submitted to near real-time verifications to detect missing data, values outside expected and logic patterns;
- Remote data monitoring is performed regularly to detect patterns of anomalies, consistency or credibility problems and other anomalies – according to pre-established queries created by the system. Any missing data or outlier is individually reviewed for inspection;
- The Coordinating Centre reviews follow-up reports regularly to ensure their consistency and completeness;
- Centre monitoring is performed while the study is being conducted. A trained professional is assigned by the Coordinating Centre to monitor the study participating centres. All the information obtained during the monitoring visits are strictly confidential.

Monitoring

Interim analyses

Since our intervention gathers the best available evidence for care of critically ill patients admitted to the ICUs, and we do not predict inherent risks in the performance of the trial, interim analyses are not planned.

Intervention Monitoring

Considering the study aim is to evaluate the impact of a complex intervention (composed by DMR, management of ICU performance indicators, and provision of clinical protocols), specific data (implementation indicators) will be collected and followed in order to ensure adherence to the protocol:

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 to study team monthly reports 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.

Power/Sample size calculation

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”.[40] Using data from 20 ICUs (10 ICUs from Ranzani et al,[41] 10 ICUs from the ORCHESTRA study,[42] available in the *ems* R package), we estimated an intraclass correlation coefficient 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. If we use a coefficient of variation of cluster size, estimated by the expected minimum and maximum method, we will maintain 80% power if the difference between the clusters minimum and maximum size is 150 patients. If needed, after the baseline period, we might review the sample calculation and simulate the power for secondary outcomes, using the data from the selected ICUs.

Analysis

All analyses will be thoroughly described in a statistical analysis plan (SAP), which will be concluded and submitted for publishing prior to database closure and the beginning of analyses. Primary statistical analyses will be performed according to the intention-to-treat principle. All outcomes at the patient-level will be performed using models that account for correlated data within each ICU (ie, ICU as a cluster) with generalised linear mixed models and adjusted by pre-specified covariates, as will be specified in the SAP. Pre-specified secondary outcomes and subgroup analyses will not be adjusted for multiple comparisons. They should, therefore, be interpreted as exploratory. We pre-specified three subgroups: type of admission (medical vs. surgical), by tertiles of SAPS3 and mechanical ventilation status (invasive MV vs. not-invasive MV). Sub-groups will be analyzed as an interaction term.

We will evaluate the calibration of the SAPS3 model 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).

ETHICS AND DISSEMINATION

The project was approved by local Research Ethics Committee (IRB) of the coordinating study centre (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. A specialist in regulatory process will oversee and support the local process. Any modifications in the protocol that might affect the development of the study and its potential benefits or safety, including changes in the objectives, design, study population, sample size, interventions or relevant management aspects, will require amendments to the protocol. Such amendments should be submitted to the IRB of the coordinating centre and all the IRBs at the participating centre for proper approval. There will be rigorous procedures of protocol version control.

The need for patients' written informed consent was waived in all 30 centres. For one centre, it was requested written informed consent for health care professionals involved in the tele-ICU visits. We obtained written agreement from the Director of each institution as well as by the ICU coordinator.[43-46]

All the information in the study will be stored (in paper and/or magnetic media) at the coordinating centre. All patient-level data will be anonymized. Access to information from the participants (during the visits) will be restricted to the intensivists performing daily rounds via Telemedicine. All records with names or other identifiers will be stored separately from the study records. Information on patients will not be disclosed except for regulatory purposes.

The TELESCOPE study Steering Committee commits to publishing the study results, whatever they may be. The results of this study will be mainly disseminated through international scientific publication. The main result of this project will be reported in an article and sub-studies are planned. Results of this project are expected to be presented in major sessions at national and international congresses, especially in the field of intensive care medicine. Study results are expected to be promoted to the lay press and disseminated in various media outlets due to its impact on the health system.

TRIAL STATUS

This paper presents the protocol for the TELESCOPE trial (original version, 1.0, approved in 07/11/2018). The baseline period started on 01/06/2019. First randomisation block and interventions started in 05/08/2019. At the time of first version of the manuscript submission, data collection for the trial was ongoing and due to be complete in December 2020.

ADDITIONAL INFORMATION

Funding

The study was conducted in partnership with the Brazilian Ministry of Health through the Institutional Development Program of the Unified Health System (PROADI - SUS, NUP 25000.018804/2018-23.), and classified in one of the objectives of the National Health Plan, highlighting the relevance and potential contribution of the project to the governance of the SUS, according to the ordinance 3.362, 12/8/2017.

Competing interests

None declared.

Patient consent

Not required.

Patient and public involvement

This research was done without patient involvement in its design or development. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. This was due to logistic limitations (critical care patients in a national wide study). Outcomes were chosen according to traditional indicators in the critical care area.

Ethics approval

This study will be conducted according to the resolution no 466/12 of the Brazilian National Health Council (http://bvsms.saude.gov.br/bvs/saudelegis/cns/2013/res0466_12_12_2012.html). The study protocol has been approved by the Research Ethics Committee of the coordinating site (approval number: CAAE 01523118.0.1001.0071) and the Research Ethics Committees of all participant institutions.

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TABLES

Table 1. Intervention framework

Component	Frequency	Tool	Goal	Attendees
Multidisciplinary rounds (DMR) by telemedicine	Daily (Monday – Friday)	Semi – structured patient electronic forms	Establish a therapeutic plan for each ICU patient	Bedside clinicians, nurse and physiotherapists
Discussion of care performance indicators performed through virtual meetings	Monthly	Report with quality indicators (monthly temporal series)	Action Plan for suboptimal quality indicators	Bedside clinicians, ICU head of department, quality improvement members

Table 2. Patient data collection schedule

	Baseline period			After randomisation		
	Admission	Daily	Discharge	Admission	Daily	Discharge
Patient details	x			x		
Pre ICU events	x			x		
Type and cause of admission	x			x		
Severity scores (SAPS 3 and SOFA)	x			x		
Comorbidities / functional status	x			x		
Treatment goals		x			x	
Organ support and devices	x	x		x	x	
Hospital-acquired infections		x			x	
Length of stay (ICU/Hospital)		x	x		x	x
Mortality and destination (ICU/Hospital)		x	x		x	x

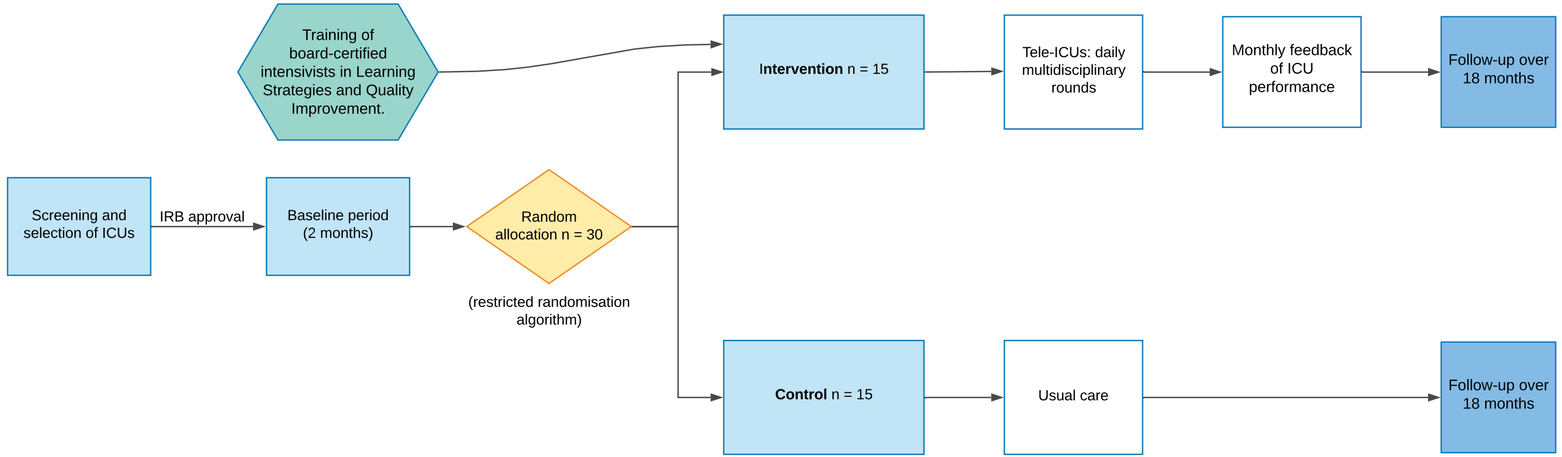
ICU: intensive care unit; SAPS 3 score: simplified acute physiology score; SOFA score: sequential organ failure assessment score.

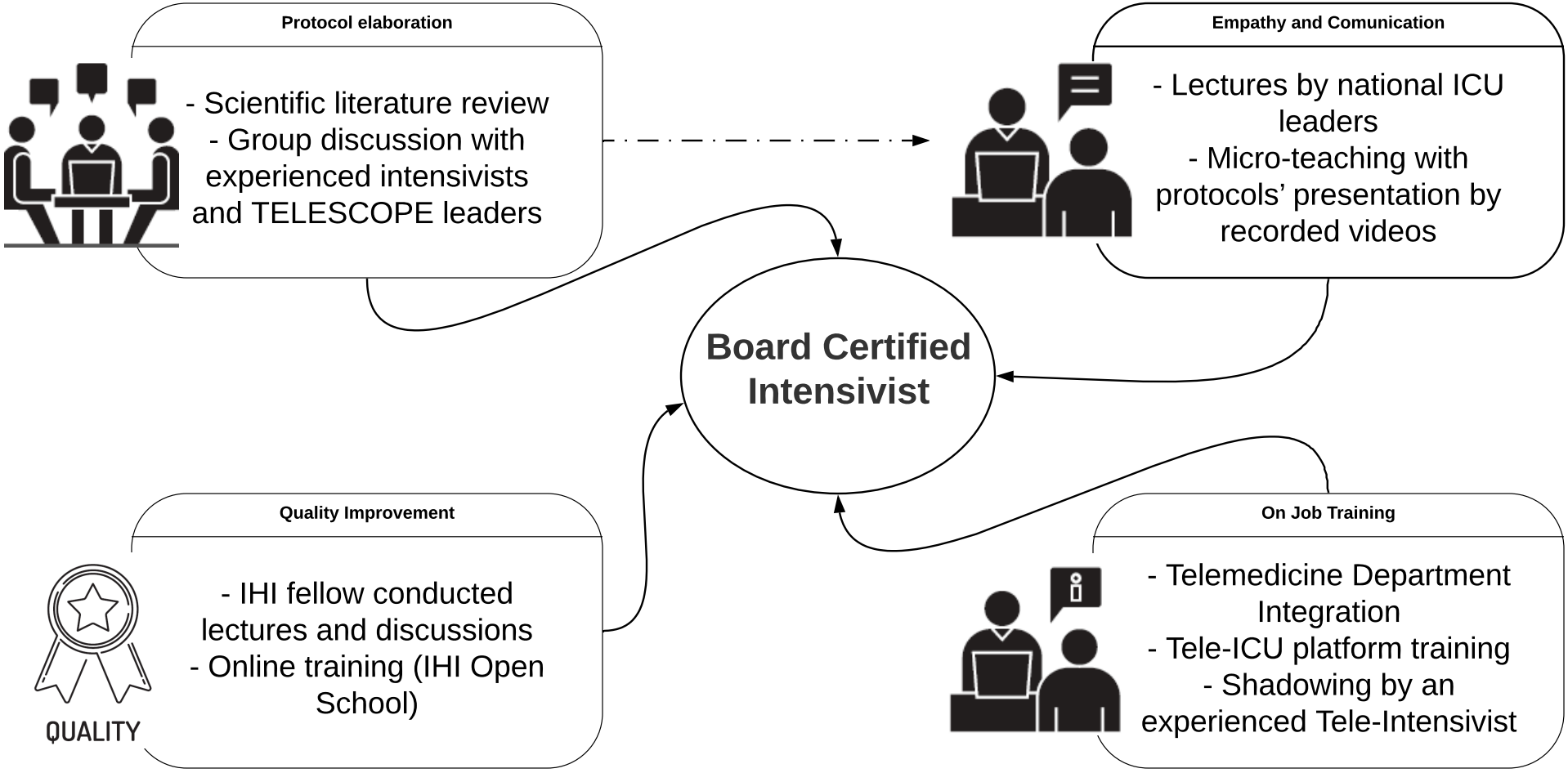
FIGURES

Figure 1. Geographic distribution of the 30 ICUs participating in the TELESCOPE trial

Figure 2. Trial timeline, randomisation, intervention and follow-up
ICU: intensive care unit; IRB: institutional review board

Figure 3. Illustration of the multicomponent training of board-certified intensivists to act in the intervention arm
ICU: intensive care unit; IHI: Institute for Healthcare Improvement


Training of board-certified intensivists in Learning Strategies and Quality Improvement.
Intervention n = 15
Tele-ICUs: daily multidisciplinary rounds
Monthly feedback of ICU performance
Follow-up over 18 months
Screening and selection of ICUs
IRB approval
Baseline period (2 months)
Random allocation n = 30
(restricted randomisation algorithm)
Control n = 15
Usual care
Follow-up over 18 months


Protocol elaboration
- Scientific literature review
- Group discussion with experienced intensivists and TELESCOPE leaders
Empathy and Comunication
- Lectures by national ICU leaders
- Micro-teaching with protocols' presentation by recorded videos
Board Certified Intensivist
Quality Improvement
QUALITY
- IHI fellow conducted lectures and discussions
- Online training (IHI Open School)
On Job Training
- Telemedicine Department Integration
- Tele-ICU platform training
- Shadowing by an experienced Tele-Intensivist

BMJ Open

TELE-critical care verSus usual Care On ICU PErformance (TELESCOPE): protocol for a cluster-randomised clinical trial on adult general ICUs in Brazil

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Health services research
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, INTENSIVE & CRITICAL CARE

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TITLE PAGE:

TELE-critical care verSus usual Care On ICU PErformance (TELESCOPE): protocol for a cluster-randomised clinical trial on adult general ICUs in Brazil

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Research registry: NCT03920501

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Contributors: DTN, OTR and AJP developed the main study intervention. DTN, OTR and AJP developed the original concept of this study. DTN, OTR, MS, ASN, TDC, RA, LC, ABC, RB, RGR, JS, LA, GS, OB, EC, LJRF and AJP contributed to study design. DTN, OTR, MS, ASN and AJP wrote the first draft of the paper, and TDC, RA, LC, ABC, RB, RGR, JS, LA, GS, OB, EC and LJRF revised the first draft. The final manuscript was reviewed by all the authors. All authors read and approved the final manuscript.

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Word count: 4239/ 4000

SYNOPSIS (*WHO Trial Registration Data Set*)

Data category	Information
Primary register and identification number	ClinicalTrials.gov - NCT03920501
Date of first registration	April 19, 2019
Secondary identification numbers	PROADI 25000.018804/2018-23
Development agency / funding source	Ministry of Health (Institutional Development Program of the Unified Health System – PROADI SUS)
Primary sponsor	Ministry of Health
Secondary sponsor	Hospital Israelita Albert Einstein
General contact	*DN*, MD, PhD. Phone: (+55) 11 96490-7494, e-mail: danilo.noritomi@einstein.br
Academic contact	*DN*, MD, PhD. Phone: (+55) 11 96490-7494, e-mail: danilo.noritomi@einstein.br
Public title	The influence of Telemedicine in the treatment of Intensive Care Unit (ICU) patients.
Academic title	Multicentric, controlled, cluster randomized superiority study to evaluate the effectiveness of specialist assistance via Telemedicine in patients admitted to ICUs in Brazilian hospitals.
Countries involved in recruitment	Brazil
Health conditions/ problems studied	ICU care design, critically ill patients, Telemedicine.
Interventions	Comparator: use of Telemedicine (intensivists) in daily ICU multidisciplinary rounds and quality indicators management (audit and feedback) Control: ICUs in the same strata, with no intervention

Data category	Information
Main inclusion and exclusion criteria	ICU clusters (all adult patients admitted after the beginning of the study will be included, with the exception of those admitted for non-medical reasons) Age: ≥ 18 years old Sex: Both Accepts volunteers: No Inclusion criteria for units: Public Hospital ICUs with a minimum of 8 hospital beds interested and committed to participating in the study. Exclusion criteria for units: Units with fully established daily multidisciplinary rounds by an intensivist, specialized units (such as ICUs admitting exclusively cardiac surgical or neurological patients) or step-down units.
Type of study	Intervention / cluster Allocation: randomization stratified by patients' previous ICU length of stay Intervention design: parallel assignment Masking: Open Primary purpose: Quality improvement
Expected date of first inclusion	February 2019
Sample size	30 clusters (15 in each group), approximately 15.000 patients
Recruitment status	Not initiated (expected for 2019)
Primary outcome	Length of stay in the ICU (days)

Data category	Information
Secondary outcomes	• Classification based on the association between standardized mortality ratio (SMR) and standardized resource use (SRU) • Rate per patient per day receiving oral or enteral nutrition • Rate per patient per day in appropriate sedation (RASS = -3 to +1) • Rate of normoxic patients on oxygen therapy (92% ≥SpO2≥96%) • Time without mechanical ventilation (MV) in 28 days • Duration of CVC use • Duration of vesical delayed probe (VDP) use • Incidence of central line-associated bloodstream infection (CLABSI) (43) • Incidence of ventilator-associated pneumonia (VAP) (44) • Incidence of catheter-associated urinary tract infection (CAUTI) (45) • Hospital Mortality

PROJECT VERSION CONTROL

Date	Comments
September 25, 2018	Original version (version 1.0)
October 09, 2020	Updated risks and benefits (version 2.0)
December 31, 2020	Enrolment period extension (version 3.0)

FUNDING/SPONSOR

The Ministry of Health (Institutional Development Program of the Unified Health System – PROADI SUS) was the primary source of funding, including costs of physician services, purchase of equipment (hardware) for Telemedicine sessions, hiring of local professionals for data collection, and travel expenses for training and monitoring. The same funding also covered costed related to the regulatory part of the study – data collection, monitoring, data curation and statistical support. The Hospital Israelita Albert Einstein allocated time of professionals and specialists who sat on the Trial Management Committee (TMC) of the study, as well as assign its Telemedicine service system. The sponsor had no role regarding design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

COMPOSITION, ROLES AND RESPONSIBILITIES

Coordinating Center: Hospital Israelita Albert Einstein (HIAE)

Executive Committee (Design and execution of the study, protocol preparation and revisions, preparation of the investigator's brochure (IB) and case reform forms (CRF), organization of the meetings of the committee of representatives of the ICUs participating in the study, oversight of the clinical trials office (ARO) management activities, publishing of study reports):

- Adriano José Pereira – intensivist. Intensive Care Unit, Hospital Israelita Albert Einstein - **Principal Investigator/Study Chair**.
- Danilo Teixeira Noritomi - intensivist. Hospital Israelita Albert Einstein, São Paulo, SP. **Senior Investigator.**
- Otavio Tavares Ranzani – intensivist and epidemiologist
- Maura Santos - Senior Nurse

Steering Committee*:*

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- Renata Albaladejo. Nurse specialist in Telemedicine
- Rodrigo Biondi – intensive care physician
- Thiago Domingos Correa – intensivist. Hospital Israelita Albert Einstein, São Paulo, SP. Member of BRICNet – Brazilian Research in Intensive Care Network

Project Office

- Composed by Main Researcher, Senior Researcher and Study Manager
- Responsible for the trial planning
- Responsible for organizing meetings with the representative committee of the ICUs participating in the trial
- Responsible for producing semiannual progress reports for the Ministry of Health and the Ethics Committee
- Responsible for the trial master file
- Responsible for managing the trial financial resources (in partnership with the PROADI institutional office) and contractual issues with third parties and individual centers

- Responsible for making recommendations for local investigators
- Responsible for semi-annual monitoring (in partnership with ARO), providing feedbacks and decisions on visits to the centers
- Responsible for data checking
- Responsible for randomization

Representative Committee of ICUs participating in the trial

- Ensure implementation of interventions at the center
- Ensure data collection quality
- Monitor trial and, if necessary, approve protocol changes or amendments/IB, ensuring the trial is conducted as efficiently as possible.

Local Investigators

- A local investigator will be appointed in each center (ICU coordinator or senior doctor at the ICU). He will oversee hired data collectors. In intervention on the ICUs, they will be responsible for ensuring the implementation of intervention proposed by a remote intensivist (Telemedicine), data collection / feeding, filling in the CRF (Case Report Form) and patient follow-up.

Data manager

- Responsible (together with Einstein's technical Telemedicine team) for maintaining patient care system, data feeding and verification.
- Responsible to execute the Data Monitoring Plan.

Sponsor (Brazil Ministry of Health)

- Approval of detailed study proposal, according to public interest
- Project schedule development follow-up (quarterly face-to-face or virtual meetings; annual written report)
- Pre-publication consent (according to current legislation)
- No participation or interference in the analyses and results.

ABSTRACT (word count: 297/300**)**

Introduction – Daily multidisciplinary rounds (DMRs) consists of systematic patient-centred discussions aiming to establish joint therapeutic goals for the next 24 hours of ICU care. The aim of the present study protocol is to evaluate whether an intervention consisting of guided DMRs, supported by a remote specialist and audit / feedback on care performance will reduce ICU length of stay compared to a control group.

Methods and analysis - A multicentre, controlled, cluster-randomised superiority trial including 30 ICUs in Brazil (15 intervention and 15 control), from August 2019 to December 2020. In a parallel assignment, ICUs are randomised to a complex-intervention composed by daily rounds carried out through Tele-ICU by a remote ICU physician; development of local quality indicators dashboards coupled with monthly meetings with local leadership; and dissemination of evidence-based clinical protocols *versus* usual care. Primary outcome is ICU length of stay. Secondary outcomes include classification of the unit according to the profiles defined by the standardized resource use and the standardized mortality rate, hospital mortality, incidence of healthcare-associated infections, ventilator-free days at 28 days, patient-days receiving oral or enteral feeding, patient-days under light sedation or alert and calm, rate of patients under normoxaemia. All adult patients admitted after the beginning of the study in each participant ICU will be enrolled. Inclusion criteria (clusters): public Brazilian ICUs with a minimum of 8 ICU beds interested/committed to participating in the study. Exclusion criteria (clusters): units with fully established daily multidisciplinary rounds by an intensivist, specialized or step-down units.

Ethics and dissemination - The study protocol was approved by the IRB of the coordinator centre, and by IRBs of each enrolled hospital/ICU. Statistical Analysis Protocol is being prepared for submission before the end of patient's enrolment. Results will be disseminated through conferences, peer-reviewed journals and to each participating unit.

Keywords: Telemedicine, Tele-ICU, Quality Improvement, Intensive Care.

ARTICLE SUMMARY:

Strengths and limitations of this study (Up to five short bullet points, no longer than one sentence each, that relate specifically to the methods)

- TELESCOPE is the first, large, multicentre cluster randomised trial performed in a middle-income country evaluating if a complex-intervention delivered mainly by TELE-ICU physician and aiming to optimize the care of critically ill patients impacts clinical outcomes.
- TELESCOPE trained general board-certified ICU physicians to deliver TELE-ICU consultancy and provide performance feedback to the attending team and managers.
- TELESCOPE used a baseline period as reference for randomisation, by using a minimization algorithm in order to achieve balance between arms and decrease within cluster variability.
- TELESCOPE intervention occurs only inside the ICU and an expected limitation is that length-of-stay depends on factors outside the ICU, such as ward bed availability.

INTRODUCTION

Healthcare demand for critically ill patients admitted to Intensive Care Units (ICUs) has been expanding worldwide, causing great social impact.[1-3] Several factors have contributed to it, such as population ageing,[4] a higher prevalence of chronic diseases, among others.[3 5] Brazil is especially sensitive to this issue as it experiences great regional disparities and population ageing without adequate control of the main health determinants.[6-9] Such situation has resulted in a large number of frail elderly, who often require critical care due to acute aggravations in chronic conditions.[10-12] This scenario combined with the risk of spending a significant amount of money with suboptimal return for the society, justifies seeking efficient care for severely ill patients.[13]

Daily multidisciplinary round (DMR) is an approach that optimizes the ICU care[14-16] DMRs consists of systematic patient-centred discussions aiming to establish joint therapeutic goals for the next 24 hours of ICU care.[14] In different studies, DMR has been associated to better clinical outcomes.[15 16] However, full implementation of DMR is still challenging, since DMR must contain several attributes in order to maximize its results: its multidisciplinary character; proper settings; time and team standardizations; definition of roles; use of guiding tools; reduction of interruptions and focus on documented objectives.[14]

Telecommunication use for health care practice, the prototype for what telemedicine has become, has been described since the advent of telecommunication.[17] The availability of high-speed data traffic has expanded the boundaries of Telemedicine, allowing the emergence of the first trial with critically ill patients in 1977.[18] In recent years, the use of Telemedicine in critically ill patients, known as tele-ICU, has gained relevance.[19] Specifically in the US, the number of ICU beds with some form of Telemedicine coverage has reached at

least 15%.[20 21] There is a variety of possible tele-ICU applications, such as second opinion consultations in specific cases, monitoring of vital signs, real-time performance and DMR conducted by a remotely located medical specialist.[22 23] . However, the benefit of tele-ICU lacks high quality scientific evidence, particularly outside high-income countries.[24 25] 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.[26] 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.

METHODS AND ANALYSIS

Aim and objectives

The TELESCOPE trial aims to answer to the following research question: Does a complex intervention offered by tele-ICU, focused on DMR attended by remote intensivists, improve ICU efficiency of adult general units in Brazil?

Primary Goal

- *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.

Secondary goals

- *To* evaluate whether an intervention consisting of guided DMRs, supported by a remote specialist (intensivist) through Telemedicine and audit / feedback on care performance improves indicators of ICU performance compared to a control group.

Study design and setting

The TELESCOPE trial is a national, multi-centre, controlled, open label, cluster randomised trial. The study tests the effectiveness of daily multidisciplinary rounds conducted by an intensivist through Telemedicine in Brazilian ICUs. Approximately 15,000 patients are expected to be recruited for a period of 18 months in 30 Brazilian ICUs (Figure 1).

After a 2-month observation period (baseline period) in which performance indicators for eligible ICUs is collected without any intervention (with the purpose of obtaining data for randomisation and characterization of the initial ICU status), the ICUs eligible for the study are randomised to either receive DMRs conducted by an intensivist through Telemedicine, from Monday to Friday, in addition to a monthly discussion of care performance indicators performed through virtual meetings (Intervention Group), or receive the unit's usual care (Control Group) (Figure 2). ICU board certified physicians receives a multicomponent training before starting the tele-ICU DMR, comprising empathy and communication and quality improvement (Figure 3). The study protocol was registered in the Clinicaltrials.Gov (NCT03920501). The study protocol follows the recommendations of the SPIRIT 2013 Statement (supplementary file 1).[27]

Intervention

Intervention group (Tele-ICU) (Table 1)

Trial intervention consists of:

1. *Daily multidisciplinary rounds* (DMR) *led by remote intensivists* - Discussions are conducted by an intensivist located in a remote centre (tele-intensivist) and the local multidisciplinary team (doctor, nurse and physiotherapist). DMRs takes place from Monday to Friday, in predetermined hours (mostly during the mornings), using

Telemedicine equipment, and approach every patient admitted to the participating ICUs. The main objective of DMR conducted by a tele-intensivist is to discuss diagnostic hypotheses, active problems and create a treatment plan until the next DMR. Tele-intensivists make recommendations based on updated scientific evidence, suitable to the local context. Clinical protocols in texts and videos 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 randomisation and establishment of a DMR routine. Electronic forms for patient follow-up serves as a guideline (Index) and are filled out by tele-intensivists. According to the current regulation (national resolution from the Brazilian Federal Council of Medicine, CFM Resolution 1643 of 2002), tele-intensivists does not act directly upon patients, but are rather mediated by the local team. Therefore, the local healthcare practitioners implement the treatment plan. Indicators of adherence to recommendations made by tele-intensivists are registered. Tele-intensivists do not write medical prescriptions, nor gives 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.

2. *Management of ICU performance* - The variables collected for the trial (table 1) are presented aggregately in reports available for each coordinator of the participating ICUs as well as for tele-intensivists. Data from Case Report Forms - CRFs (REDCap®, Vanderbilt University Medical Center, TN, USA) are used to automatically feed dashboards in real-time, specially developed for this purpose (R Studio/Shiny®,

Boston, MA, USA). In addition, 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 randomised 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, these data are not available for the care team nor to the coordination of the participating ICUs.

Sites

The list of potential units was retrieved from the national registry of health facilities ("Cadastro Nacional de Estabelecimentos de Saúde – CNES", in Portuguese), filtering those facilities with at least 8 ICU adult beds available.

Inclusion/Exclusion

The ICUs are invited by electronic means for an interview in which the eligibility and feasibility criteria below will be verified.

Inclusion criteria for ICUs

- ICUs of public or philanthropic hospitals
- ICUs with a minimum of 8 ICU beds
- ICUs with on-site registered doctors and nurses

Exclusion criteria for ICUs

- ICUs that already presented DMRs, defined as:

  - 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

  - Monthly management of indicators (audit and feedback) with specific planning.

- Specialized ICUs (ICUs admitting exclusively cardiac surgery, neurological, burned patients).
- Step-down units or coronary units

Patients

All consecutive patients that fulfil the inclusion criteria and none of the exclusion criteria will be enrolled.

Inclusion/Exclusion

The patients admitted in the ICU who currently meet the following inclusion criteria are included:

- Age ≥18 years old
- Patients admitted to the ICU after the beginning of the trial

Exclusion criteria for patients

- Patients admitted to the ICU due to justice-related issues (since in such circumstances the ICU admission or discharge may be determined by law and not medical reasons)
- Patients previously included in the TELESCOPE trial (for the analysis of the primary outcome).

Randomisation

The 30 ICUs are randomly assigned to either the intervention group (n=15) or the control group (n=15) using a restricted randomisation approach to ensure balance across the groups *using the following variables at the ICU level: number of ICU beds, mean SAPS 3, mean ICU LOS, SMR, SRU, and a dummy indicator for Brazilian region where the ICU is located (South/Southeast x North/Northeast/Central-West)*.[28 29] The randomisation unit will be the ICU to avoid contamination of the intervention. Only one ICU per hospital will be included in the trial. The randomisation is performed in blocks, sizes of 14, 7 and 9, following the completion of the baseline period. To ensure allocation concealment, the statistician responsible for the randomisation list receives only the ICU identifier code, being unaware of which unit it refers to. The allocation list is sent to the study coordinator, who informs the ICUs about the randomisation. The allocation will be maintained until the end of the study.

Blinding

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 of the DMRs and monthly feedback/audit meetings.

Follow-up

Patients are followed up until hospital discharge by the health care worker responsible for data collection.

Outcomes

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 time of transfer to another care facility or another hospital, 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.

Secondary exploratory outcomes

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

- Classification of the unit according to the profiles defined by the standardized resource use (SRU) and the standardized mortality rate (SMR).[30] The SRU reflects the observed / expected rate of resources used (estimated as ICU length of stay for surviving patients), adjusted by patient's severity of illness.[31 32] 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 four groups: "most efficient" (SMR and SRU <

median); "least efficient" (SMR, SRU > median); "overachieving" (low SMR, high SRU), "underachieving" (high SMR, low SRU)[31]

- In-hospital mortality, defined as death by any cause from date of ICU admission until the date of hospital discharge or death, whichever comes first
- Incidence of central line-associated bloodstream infection (CLABSI), as defined by the CDC[33]
- Incidence of ventilator-associated event (VAE), as defined by the CDC[34]
- Incidence of catheter-associated urinary tract infection (CAUTI), as defined by the CDC[35]
- 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
- Patient-days receiving oral or enteral feeding, defined as any amount oral or enteral diet
- Patient-days under light sedation or alert and calm [Richmond Agitation-Sedation Scale (RASS) = -3 to +1]
- Rate of patients under normoxaemia [peripheral oxygen saturation (SpO_2) between 92% and 96%]

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
- Compliance to head of bed elevation for patient under MV
- Rate of central venous catheter (CVC) use and duration
- Rate of urinary catheter use and duration
- Adequate prevention of venous thromboembolism (VTE)
- Rate of patients with adequate glycaemic control

We will truncate the primary and secondary outcomes follow-up at 90 days.

Data collection

At the patient level, the following data is collected (Table 2):

At the time of ICU admission:

- Identifier, date of birth, gender, main reason of ICU admission (adapted from APACHE III),[36] readmission status
- Anthropometric characteristics, comorbidities (adapted from SAPS3),[37] functional status (adapted from ECOG)[37]
- Respiratory, cardiovascular, and renal support
- Diet and sedation status
- Presence of devices: central venous catheter, arterial line, permanent catheters, urinary catheter, oro/naso-tracheal catheter and traqueostomy
- Date and time of hospital admission
- Date and time of ICU admission

- Simplified Acute Physiology (SAPS 3) score[32]
- Sequential organ failure assessment (SOFA) score[38 39]

Throughout the ICU admission:

- Documented goals from the DMR
- Documented discharge order status, defined as any mention to readiness to discharge or ICU transference order
- MV status and mechanical ventilation parameters
- SpO_2 range for patients on oxygen therapy
- Head of bed elevation for patients under MV
- Spontaneous respiratory test, accidental extubation or re-intubation events
- Need of vasoactive drugs and renal replacement therapy
- Continuous sedative infusion and light sedation strategy (reduction/daily interruption)
- Daily value (categorized below, above or within -3 to +1 range) of the RASS for patients undergoing continuous sedation at a predetermined time
- Adequacy of VTE prophylaxis: considered adequate when patient is bedridden without any of the following exclusion criteria: active bleeding, stress gastric ulcer, uncontrolled arterial hypertension (>180/110 mmHg), coagulation disorder, allergy, kidney failure (Cl<30 ml/min), ocular or cranial surgery in last 2 weeks, and lumbar puncture in last 24h).
- Presence of oral or enteral nutrition
- Glycemic control: considered adequate if between 60 to 180 mg/dL

- Notification of health-care-related infection episodes according to CDC (Centers for Disease Control and Prevention) criteria:
    - Central-line associated bloodstream infection (CLABSI)[33]
    - Ventilator-associated events (VAE)[34]
    - Catheter-associated urinary tract infection (CAUTI)[35]
    - Date and time of central venous catheter (CVC) insertion for patients undergoing CVC insertion
- Date and time of withdrawal of CVC for patients undergoing CVC insertion
- Date and time of indwelling urinary catheter (IUC) insertion for patients submitted to IUC insertion
- Date and time of withdrawal of IUC for patients undergoing IUC insertion
- Documentation of decisions for limiting the life support considering any mention to withholding or withdrawing in the medical records

At the time of ICU discharge

- Date and time of ICU discharge
- ICU outcome: discharge to ward, hospital transfer, death

At the time of hospital discharge

- Date and time of hospital discharge
- Hospital outcome: hospital transfer, death

Data collection and management

Trained health care workers collect data, without any involvement from the study committees and investigators. We developed a standard CRFs for the trial, with extensive validation and piloting aiming clarity and consistency.

Data is input 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. Medical data from tele-intensivist consultations is generated and stored using a specific platform developed by the Tele-ICU Department of the Hospital Israelita Albert Einstein/São Paulo - Brazil. Images and audio are never saved or stored. The electronic files are stored in the hospital's servers in a controlled and secure environment to guarantee confidentiality. Furthermore, access to all documents is user and password controlled. To ensure data quality, the following procedures are performed:

- All professionals responsible for data collection are trained before the beginning of the trial in order to guarantee clear definitions for accurate data collection;
- A research nurse from the Coordinating Centre is available 24/7 to solve any problem and question about data collection;
- Data input in the system are submitted to near real-time verifications to detect missing data, values outside expected and logic patterns;
- Remote data monitoring is performed regularly to detect patterns of anomalies, consistency or credibility problems and other anomalies – according to pre-established queries created by the system. Any missing data or outlier is individually reviewed for inspection;
- The Coordinating Centre reviews follow-up reports regularly to ensure their consistency and completeness;

- Centre monitoring is performed while the study is being conducted. A trained professional is assigned by the Coordinating Centre to monitor the study participating centres. All the information obtained during the monitoring visits are strictly confidential.

Monitoring

Interim analyses

Since our intervention gathers the best available evidence for care of critically ill patients admitted to the ICUs, and we do not predict inherent risks in the performance of the trial, interim analyses are not planned. Therefore, a formal Data Monitoring Committee was deemed unneeded. Adverse events are not expected to occur but could be reported by local researchers, data assistants, and local doctors.

Intervention Monitoring

Considering the study aim is to evaluate the impact of a complex intervention (composed by DMR, management of ICU performance indicators, and provision of clinical protocols), specific data (implementation indicators) will be collected and followed in order to ensure adherence to the protocol:

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 to study team monthly reports 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.

Auditing

Trial conduct is subjected to audit by Einstein Research Integrity Committee, at any time, independently of the IRB and research team, the same way as any interventional studies performed at Albert Einstein Hospital (random selection).

Power/Sample size calculation

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".[40] Using data from 20 ICUs (10 ICUs from Ranzani et al,[41] 10 ICUs from the ORCHESTRA study,[42] available in the *ems* R package), we estimated an intraclass correlation coefficient 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. If we use a coefficient of variation of cluster size, estimated by the expected minimum and maximum method, we will maintain 80% power if the difference between the clusters minimum and maximum size is 150 patients. If needed, after the baseline period, we might review the sample calculation and simulate the power for secondary outcomes, using the data from the selected ICUs.

Analysis

All analyses will be thoroughly described in a statistical analysis plan (SAP), which will be concluded and submitted for publishing prior to database closure and the beginning of analyses. Primary statistical analyses will be performed according to the intention-to-treat principle. All outcomes at the patient-level will be performed using models that account for correlated data within each ICU (ie, ICU as a cluster) with generalised linear mixed models and adjusted by pre-specified covariates, as will be specified in the SAP. Pre-specified secondary outcomes and subgroup analyses will not be adjusted for multiple comparisons. They should, therefore, be interpreted as exploratory. We pre-specified three subgroups: type of admission (medical vs. surgical), by tertiles of SAPS3 and mechanical ventilation status (invasive MV vs. not-invasive MV). Sub-groups will be analyzed as an interaction term.

We will evaluate the calibration of the SAPS3 model 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).

ETHICS AND DISSEMINATION

The project was approved by local Research Ethics Committee (IRB) of the coordinating study centre (Hospital Israelita Albert Einstein) (CAAE: 01523118.0.1001.0071) and by the local IRB from each one of the 30 ICUs (supplementary file 2), following the Brazilian legislation. A specialist in regulatory process will oversee and support the local process. Any modifications in the protocol that might affect the development of the study and its potential benefits or safety, including changes in the objectives, design, study population, sample size, interventions or relevant management aspects, will require amendments to the protocol. Such amendments should be submitted to the IRB of the

coordinating centre and all the IRBs at the participating centre for proper approval. There will be rigorous procedures of protocol version control.

The need for patients' written informed consent was waived in all 30 centres. For one centre, it was requested written informed consent for health care professionals involved in the tele-ICU visits. We obtained written agreement from the Director of each institution as well as by the ICU coordinator.[43-46]

Therefore, the set interventions are not specifically directed to the patients but to the whole cluster together: the ICU (intervention type A).[47] In this type of interventions, there is only one decision to be made for each cluster and individual choice are not appropriated.[47] In this sense, informed consent was proposed and signed in the cluster-level. In the best interest of patients, medical teams and other professionals, the Hospital Director and the Head of ICU (Physician) were the responsible to sign the consent form. This proposal was approved by all the involved IRBs (coordinating centre and the IRBs of each one of the 30 participant hospitals).

All the information in the study will be stored (in paper and/or magnetic media) at the coordinating centre. All patient-level data will be anonymized, and will be accessed only by the data manager and statistician. Access to information from the participants (during the visits) will be restricted to the intensivists performing daily rounds via Telemedicine. All records with names or other identifiers will be stored separately from the study records. Information on patients will not be disclosed except for regulatory purposes.

The TELESCOPE study Steering Committee commits to publishing the study results, whatever they may be. The results of this study will be mainly disseminated through international scientific publication. The main result of this project will be reported in an article and sub-studies are planned. Results of this project are expected to be presented in

major sessions at national and international congresses, especially in the field of intensive care medicine. Study results are expected to be promoted to the lay press and disseminated in various media outlets due to its impact on the health system.

TRIAL STATUS

This paper presents the protocol for the TELESCOPE trial (original version, 1.0, approved in 07/11/2018). The baseline period started on 01/06/2019. First randomisation block and interventions started in 05/08/2019. At the time of first version of the manuscript submission, data collection for the trial was ongoing and due to be complete in the first semester of 2021.

ADDITIONAL INFORMATION

Funding

The study was conducted in partnership with the Brazilian Ministry of Health through the Institutional Development Program of the Unified Health System (PROADI - SUS, NUP 25000.018804/2018-23.), and classified in one of the objectives of the National Health Plan, highlighting the relevance and potential contribution of the project to the governance of the SUS, according to the ordinance 3.362, 12/8/2017.

Authorship

Authorship will follow current guidelines of International Committee of Medical Journal Editors (ICMJE). Executive and Steering Committee are planned to be list as authors/co-authors, since fulfilling authorship criteria (substantive contributions to the design, conduct, interpretation, and reporting of a clinical trial). If some protocol authors are not named

author info publications (not fulfil such criteria), their names will be acknowledged in the reports. Three main papers are planned: Protocol paper, Statistical Analysis Plan, Main Paper (trial results). Principal Investigator - AJP, Senior Researcher - DTN and OTR - Statistician Specialist will share and alternate in first, second and last positions. Local PIs will be cited as collaborators in the main paper. The same is planned for abstracts or oral presentations in international meetings. Disputes regarding authorship will be settled by the Study Chair and Executive Committee. Professional writer's participations are not planned.

Competing interests

None declared.

Patient consent

Not required.

Patient and public involvement

This research was done without patient involvement in its design or development. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. This was due to logistic limitations (critical care patients in a national wide study). Outcomes were chosen according to traditional indicators in the critical care area.

Ethics approval

This study will be conducted according to the resolution no 466/12 of the Brazilian National Health Council (http://bvsms.saude.gov.br/bvs/saudelegis/cns/2013/res0466_12_12_2012.html). The

study protocol has been approved by the Research Ethics Committee of the coordinating site (approval number: CAAE 01523118.0.1001.0071) and the Research Ethics Committees of all participant institutions (supplementary file 2).

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TABLES

Table 1. Intervention framework

Component	Frequency	Tool	Goal	Attendees
Multidisciplinary rounds (DMR) by telemedicine	Daily (Monday – Friday)	Semi – structured patient electronic forms	Establish a therapeutic plan for each ICU patient	Bedside clinicians, nurse and physiotherapists
Discussion of care performance indicators performed through virtual meetings	Monthly	Report with quality indicators (monthly temporal series)	Action Plan for suboptimal quality indicators	Bedside clinicians, ICU head of department, quality improvement members

Table 2. Patient data collection schedule

	Baseline period			After randomisation		
	Admission	Daily	Discharge	Admission	Daily	Discharge
Patient details	x			x		
Pre ICU events	x			x		
Type and cause of admission	x			x		
Severity scores (SAPS 3 and SOFA)	x			x		
Comorbidities / functional status	x			x		
Treatment goals		x			x	
Organ support and devices	x	x		x	x	
Hospital-acquired infections		x			x	
Length of stay (ICU/Hospital)		x	x		x	x
Mortality and destination (ICU/Hospital)		x	x		x	x

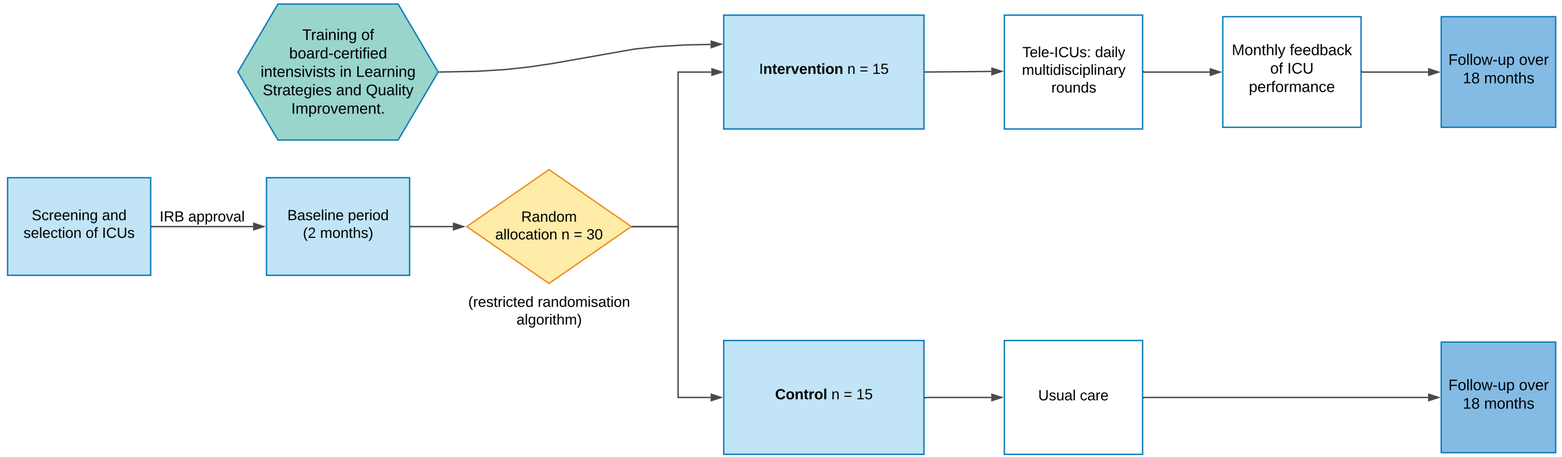
ICU: intensive care unit; SAPS 3 score: simplified acute physiology score; SOFA score: sequential organ failure assessment score.

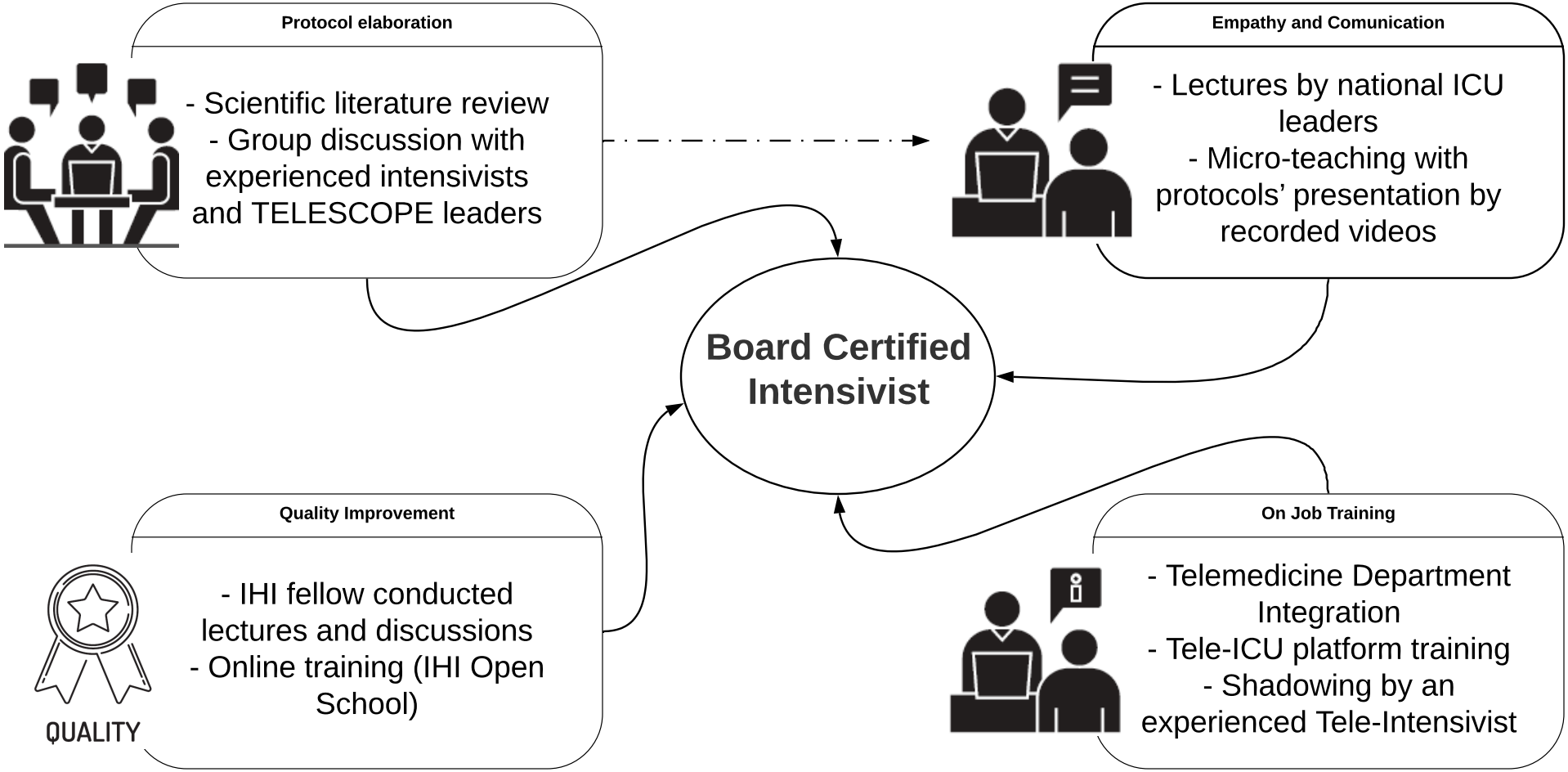
FIGURES

Figure 1. Geographic distribution of the 30 ICUs participating in the TELESCOPE trial

Figure 2. Trial timeline, randomisation, intervention and follow-up
ICU: intensive care unit; IRB: institutional review board

Figure 3. Illustration of the multicomponent training of board-certified intensivists to act in the intervention arm
ICU: intensive care unit; IHI: Institute for Healthcare Improvement


Training of board-certified intensivists in Learning Strategies and Quality Improvement.
Intervention n = 15
Tele-ICUs: daily multidisciplinary rounds
Monthly feedback of ICU performance
Follow-up over 18 months
Screening and selection of ICUs
IRB approval
Baseline period (2 months)
Random allocation n = 30
(restricted randomisation algorithm)
Control n = 15
Usual care
Follow-up over 18 months


Protocol elaboration
- Scientific literature review
- Group discussion with experienced intensivists and TELESCOPE leaders
Empathy and Comunication
- Lectures by national ICU leaders
- Micro-teaching with protocols' presentation by recorded videos
Board Certified Intensivist
Quality Improvement
QUALITY
- IHI fellow conducted lectures and discussions
- Online training (IHI Open School)
On Job Training
- Telemedicine Department Integration
- Tele-ICU platform training
- Shadowing by an experienced Tele-Intensivist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	01
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	01
	2b	All items from the World Health Organization Trial Registration Data Set	02-04
Protocol version	3	Date and version identifier	01 and 05
Funding	4	Sources and types of financial, material, and other support	01
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	01
	5b	Name and contact information for the trial sponsor	01
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	06
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	07-10

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	13-14
	6b	Explanation for choice of comparators	15-17
Objectives	7	Specific objectives or hypotheses	14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	14-15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14-15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17-18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	25-26
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-21

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15 (Figure 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	26
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18-19
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	18-19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	19
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	21-24

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	24-25
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24-25
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	26-27
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	26
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	26
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	25
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	26
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	27-28

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	27-28
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	27-28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	28
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	29
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	28
	31b	Authorship eligibility guidelines and any intended use of professional writers	28
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Supplementary File 2. Research ethics committees of the TELESCOPE trial.

Centre	HOSPITAL (Brazilian estate)	RESEARCH ETHICS COMMITTEE	APPROVAL NUMBER
Coordinator	Hospital Albert Einstein (SP)	Hospita Israelita Albert Einstein HIAE	CAAE 01523118.0.1001.0071
Centre 1	Hospital Universitário da Universidade Federal de Sergipe (SE)	Universidade Federal de Sergipe UFS	CAAE 01523118.0.2005.5546
Centre 2	Hospital Municipal Senhora Santana (Hospital Microrregional) (MG)	Faculdade de Talentos Humanos - FACTHUS	CAAE 01523118.0.2001.9028
Centre 3	Santa Casa de Paranavaí (PR)	Universidade Estadual do Parana UNESPAR	CAAE 01523118.0.2025.9247
Centre 4	Hospital de Caridade de Irati (PR)	Universidade Estadual do Centro Oeste - Campus de Irati - UNICENTRO	CAAE 01523118.0.2015.8967
Centre 5	Hospital Regional de Gurupi (TO)	Centro Universitario UNIRG	CAAE 01523118.0.2026.5518
Centre 6	Hospital Nossa Senhora da Oliveira – HNSO (RS)	Comitê de Ética em Pesquisa do Hospital Nossa Senhora de Pompéia	CAAE 01523118.0.2023.5331
Centre 7	Hospital de Trauma Dom Luiz Gonzaga Fernandes (PB)	Secretaria de Saude do Estado da Paraíba	CAAE 01523118.0.2033.5186
Centre 8	Hospital Regional de Assis (SP)	Hospital Regional do Câncer de Presidente Prudente HRCPP	CAAE 01523118.0.2012.8247
Centre 9	Hospital Municipal de Paracatu (MG)	Faculdade deeCiências e Educação Sena Aires	CAAE 01523118.0.2010.5595
Centre 10	Hospital Regional Dr. Clodolfo Rodrigues de Melo (AL)	Universidade Federal de Alagoas	CAAE 01523118.0.2029.5013
Centre 11	Hospital Municipal Rocha Faria (RJ)	Secretaria Municipal de Saúde do Rio de Janeiro - SMS/RJ	CAAE 01523118.0.2021.5279
Centre 12	Hospital Universitario Nova Esperança (PB)	Escola de Enfermagem Nova Esperança LTDA	CAAE 01523118.0.2013.5179
Centre 13	Santa Casa de Itapetininga (SP)	Faculdade de Ciências Médicas e da Saúde da Pontifícia Universidade Católica de São Paulo - FCMS-PUC/SP	CAAE 1523118.0.2038.5373
Centre 14	Casa de Caridade de Muriaé - Hospital São Paulo (MG)	Hospital Santa Paula - SP	CAAE 01523118.0.2036.5670
Centre 15	Santa Casa de Misericórdia de Votuporanga (SP)	CEP UNIFEV	CAAE 01523118.0.2006.0078
Centre 16	Irmandade da Santa Casa de Sorocaba (SP)	Universidade de Sorocaba UNISO	CAAE 01523118.0.2022.5500
Centre 17	Santa Casa de Misericórdia de Belo Horizonte (MG)	Santa Casa de Misericórdia de Belo Horizonte - SCMBH	CAAE 01523118.0.2008.5138
Centre 18	Hospital da Restauração - Secretaria Estadual de Saúde (PE)	Hospital da Restauração - PE CEP/HUOC/PROCAPE	CAAE 01523118.0.2004.5198
Centre 19	Hospital Geral de Roraima (RR)	Universidade Federal de Roraima - UFRR	CAAE 01523118.0.2011.5302
Centre 20	Hospital Geral de Vitória da Conquista (BA)	Secretaria da Saude do Estado da Bahia - SESAB	CAAE 01523118.0.2009.0052
Centre 21	Hospital Regional Justino Luz (PI)	Hospital Universitário da Universidade Federal do Piauí UFPI	CAAE 01523118.0.2030.8050

Centre 22	Complexo Hospitalar Mangabeira Governador Tarcísio Burity (PB)	UFPB - Centro de Ciências da Saúde da Universidade Federal da Paraíba UFPB	CAAE 01523118.0.2003.5188
Centre 23	Hospital Regional de Barbacena Dr. José Américo (MG)	Fundação Hospitalar do Estado de Minas Gerais FHEMIG	CAAE 01523118.0.2024.5119
Centre 24	Hospital Geral de Promissão Prefeito Miguel Martin Gualda (SP)	Hospital Regional do Câncer de Presidente Prudente HRCPP	CAAE 01523118.0.2037.8247
Centre 25	Hospital Maternidade e Pronto Socorro Santa Lúcia LTDA (MG)	Hospital Vera Cruz HVC/ MG	CAAE 01523118.0.2002.5135
Centre 26	Hospital Municipal Padre Germano Lauck - Hospital Municipal de Foz do Iguaçu (PR)	Centro Universitário Dinânica das Cataratas UDC	CAAE 01523118.0.2007.8527
Centre 27	Santa Casa de Anápolis (GO)	UEG - Universidade Estadual de Goiás	CAAE 01523118.0.2031.8113
Centre 28	Santa Casa de Misericordia de Passos (MG)	Santa Casa de Misericordia de Passos SCMP	CAAE 01523118.0.2014.8043
Centre 29	Hospital Geral e Maternidade Tereza Ramos (SC)	Secretaria de Estado da Saúde de Santa Catarina/SES	CAAE 01523118.0.2016.0115
Centre 30	Hospital Regional do Paranoá (DF)	Comitê de Ética em Pesquisa FEPECS/SES-DF	CAAE 01523118.0.2019.5553

BMJ Open

TELE-critical care verSus usual Care On ICU PErformance (TELESCOPE): protocol for a cluster-randomised clinical trial on adult general ICUs in Brazil

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Health services research
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, INTENSIVE & CRITICAL CARE

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TITLE PAGE:

TELE-critical care verSus usual Care On ICU PErformance (TELESCOPE): protocol for a cluster-randomised clinical trial on adult general ICUs in Brazil

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COMPOSITION, ROLES AND RESPONSIBILITIES

Coordinating Center: Hospital Israelita Albert Einstein (HIAE)

Executive Committee (Design and execution of the study, protocol preparation and revisions, preparation of the investigator's brochure (IB) and case reform forms (CRF), organization of the meetings of the committee of representatives of the ICUs participating in the study, oversight of the clinical trials office (ARO) management activities, publishing of study reports):

- Adriano José Pereira – intensivist. Intensive Care Unit, Hospital Israelita Albert Einstein - **Principal Investigator/Study Chair**.
- Danilo Teixeira Noritomi - intensivist. Hospital Israelita Albert Einstein, São Paulo, SP. **Senior Investigator.**
- Otavio Tavares Ranzani – intensivist and epidemiologist
- Maura Santos - Senior Nurse

Steering Committee:

- Adriano José Pereira – intensivist. Intensive Care Unit, Hospital Israelita Albert Einstein - **Principal Investigator/Study Chair**.
- Alexandre Biasi Cavalcanti – intensivist. Research Institute HCor, São Paulo, SP. Member of BRICNet – Brazilian Research in Intensive Care Network
- Ary Serpa Neto – intensivist. Hospital Alemão Oswaldo Cruz, São Paulo, SP. Member of BRICNet – Brazilian Research in Intensive Care Network
- Danilo Teixeira Noritomi - intensivist. Hospital Israelita Albert Einstein, São Paulo, SP. **Senior Investigator.**
- Eduardo Cordioli. Health Care Manager of the Department of Telemedicine of the Hospital Israelita Albert Einstein, São Paulo, SP
- Fernando Gatti. Coordinator of the Hospital Infection Control Service of the Hospital Israelita Albert Einstein, São Paulo, SP – 10
- Jorge Salluh. Intensivist. Professor in the UFRJ Graduate Program, Researcher of the Intensive Care Department, IDOR- Rio de Janeiro

- Leonardo José Rolin Ferraz – intensivist. Intensive Care Unit, Hospital Israelita Albert Einstein
- Lúbia Caus. Intensivist. Intensive Care Unit, Hospital Israelita Albert Einstein.
- Luciano Azevedo – intensivist. Hospital Sírio-Libanês & Hospital São Paulo, UNIFESP, São Paulo, SP. Member of BRICNet – Brazilian Research in Intensive Care Network
- Maura Cristina Santos. Senior nurse of the Department of Severely ill Patients, tele – ICU. Study Manager
- Otávio Berwanger – epidemiologist. Hospital Israelita Albert Einstein, São Paulo, SP
- Otavio Tavares Ranzani – intensivist and epidemiologist
- Regis Goulart Rosa – intensivist. Adult Intensive Care Unit of the Hospital Moinhos de Vento, Porto Alegre, RS
- Renata Albaladejo. Nurse specialist in Telemedicine
- Rodrigo Biondi – intensive care physician
- Thiago Domingos Correa – intensivist. Hospital Israelita Albert Einstein, São Paulo, SP. Member of BRICNet – Brazilian Research in Intensive Care Network

Project Office

- Composed by Main Researcher, Senior Researcher and Study Manager
- Responsible for the trial planning
- Responsible for organizing meetings with the representative committee of the ICUs participating in the trial
- Responsible for producing semiannual progress reports for the Ministry of Health and the Ethics Committee
- Responsible for the trial master file
- Responsible for managing the trial financial resources (in partnership with the PROADI institutional office) and contractual issues with third parties and individual centers

- Responsible for making recommendations for local investigators
- Responsible for semi-annual monitoring (in partnership with ARO), providing feedbacks and decisions on visits to the centers
- Responsible for data checking
- Responsible for randomization

Representative Committee of ICUs participating in the trial

- Ensure implementation of interventions at the center
- Ensure data collection quality
- Monitor trial and, if necessary, approve protocol changes or amendments/IB, ensuring the trial is conducted as efficiently as possible.

Local Investigators

- A local investigator will be appointed in each center (ICU coordinator or senior doctor at the ICU). He will oversee hired data collectors. In intervention on the ICUs, they will be responsible for ensuring the implementation of intervention proposed by a remote intensivist (Telemedicine), data collection / feeding, filling in the CRF (Case Report Form) and patient follow-up.

Data manager

- Responsible (together with Einstein's technical Telemedicine team) for maintaining patient care system, data feeding and verification.
- Responsible to execute the Data Monitoring Plan.

Sponsor (Brazil Ministry of Health)

- Approval of detailed study proposal, according to public interest
- Project schedule development follow-up (quarterly face-to-face or virtual meetings; annual written report)
- Pre-publication consent (according to current legislation)
- No participation or interference in the analyses and results.

ABSTRACT (word count: 297/300**)**

Introduction – Daily multidisciplinary rounds (DMRs) consists of systematic patient-centred discussions aiming to establish joint therapeutic goals for the next 24 hours of ICU care. The aim of the present study protocol is to evaluate whether an intervention consisting of guided DMRs, supported by a remote specialist and audit / feedback on care performance will reduce ICU length of stay compared to a control group.

Methods and analysis - A multicentre, controlled, cluster-randomised superiority trial including 30 ICUs in Brazil (15 intervention and 15 control), from August 2019 to June 2021. In a parallel assignment, ICUs are randomised to a complex-intervention composed by daily rounds carried out through Tele-ICU by a remote ICU physician; development of local quality indicators dashboards coupled with monthly meetings with local leadership; and dissemination of evidence-based clinical protocols *versus* usual care. Primary outcome is ICU length of stay. Secondary outcomes include classification of the unit according to the profiles defined by the standardized resource use and the standardized mortality rate, hospital mortality, incidence of healthcare-associated infections, ventilator-free days at 28 days, patient-days receiving oral or enteral feeding, patient-days under light sedation or alert and calm, rate of patients under normoxaemia. All adult patients admitted after the beginning of the study in each participant ICU will be enrolled. Inclusion criteria (clusters): public Brazilian ICUs with a minimum of 8 ICU beds interested/committed to participating in the study. Exclusion criteria (clusters): units with fully established daily multidisciplinary rounds by an intensivist, specialized or step-down units.

Ethics and dissemination - The study protocol was approved by the IRB of the coordinator centre, and by IRBs of each enrolled hospital/ICU. Statistical Analysis Protocol is being prepared for submission before the end of patient's enrolment. Results will be disseminated through conferences, peer-reviewed journals and to each participating unit.

Keywords: Telemedicine, Tele-ICU, Quality Improvement, Intensive Care.

ARTICLE SUMMARY:

Strengths and limitations of this study (Up to five short bullet points, no longer than one sentence each, that relate specifically to the methods)

- TELESCOPE is the first, large, multicentre cluster randomised trial performed in a middle-income country evaluating if a complex-intervention delivered mainly by TELE-ICU physician and aiming to optimize the care of critically ill patients impacts clinical outcomes.
- TELESCOPE trained general board-certified ICU physicians to deliver TELE-ICU consultancy and provide performance feedback to the attending team and managers.
- TELESCOPE used a baseline period as reference for randomisation, by using a minimization algorithm in order to achieve balance between arms and decrease within cluster variability.
- TELESCOPE intervention occurs only inside the ICU and an expected limitation is that length-of-stay depends on factors outside the ICU, such as ward bed availability.

INTRODUCTION

Healthcare demand for critically ill patients admitted to Intensive Care Units (ICUs) has been expanding worldwide, causing great social impact.[1-3] Several factors have contributed to it, such as population ageing,[4] a higher prevalence of chronic diseases, among others.[3 5] Brazil is especially sensitive to this issue as it experiences great regional disparities and population ageing without adequate control of the main health determinants.[6-9] Such situation has resulted in a large number of frail elderly, who often require critical care due to acute aggravations in chronic conditions.[10-12] This scenario combined with the risk of spending a significant amount of money with suboptimal return for the society, justifies seeking efficient care for severely ill patients.[13]

Daily multidisciplinary round (DMR) is an approach that optimizes the ICU care[14-16] DMRs consists of systematic patient-centred discussions aiming to establish joint therapeutic goals for the next 24 hours of ICU care.[14] In different studies, DMR has been associated to better clinical outcomes.[15 16] However, full implementation of DMR is still challenging, since DMR must contain several attributes in order to maximize its results: its multidisciplinary character; proper settings; time and team standardizations; definition of roles; use of guiding tools; reduction of interruptions and focus on documented objectives.[14]

Telecommunication use for health care practice, the prototype for what telemedicine has become, has been described since the advent of telecommunication.[17] The availability of high-speed data traffic has expanded the boundaries of Telemedicine, allowing the emergence of the first trial with critically ill patients in 1977.[18] In recent years, the use of Telemedicine in critically ill patients, known as tele-ICU, has gained relevance.[19] Specifically in the US, the number of ICU beds with some form of Telemedicine coverage has reached at

least 15%.[20 21] There is a variety of possible tele-ICU applications, such as second opinion consultations in specific cases, monitoring of vital signs, real-time performance and DMR conducted by a remotely located medical specialist.[22 23] . However, the benefit of tele-ICU lacks high quality scientific evidence, particularly outside high-income countries.[24 25] 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.[26] 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.

METHODS AND ANALYSIS

Aim and objectives

The TELESCOPE trial aims to answer to the following research question: Does a complex intervention offered by tele-ICU, focused on DMR attended by remote intensivists, improve ICU efficiency of adult general units in Brazil?

Primary Goal

- *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.

Secondary goals

- *To* evaluate whether an intervention consisting of guided DMRs, supported by a remote specialist (intensivist) through Telemedicine and audit / feedback on care performance improves indicators of ICU performance compared to a control group.

Study design and setting

The TELESCOPE trial is a national, multi-centre, controlled, open label, cluster randomised trial. The study tests the effectiveness of daily multidisciplinary rounds conducted by an intensivist through Telemedicine in Brazilian ICUs. Approximately 15,000 patients are expected to be recruited for a period of 18 months in 30 Brazilian ICUs (Figure 1). The main characteristics of the TELESCOPE trial, according to World Health Organization standards, are summarized in the Synopsis table (table 1). The three versions of the protocol are listed in the project control version table (table 2).

After a 2-month observation period (baseline period) in which performance indicators for eligible ICUs is collected without any intervention (with the purpose of obtaining data for randomisation and characterization of the initial ICU status), the ICUs eligible for the study are randomised to either receive DMRs conducted by an intensivist through Telemedicine, from Monday to Friday, in addition to a monthly discussion of care performance indicators performed through virtual meetings (Intervention Group), or receive the unit's usual care (Control Group) (Figure 2). ICU board certified physicians receives a multicomponent training before starting the tele-ICU DMR, comprising empathy and communication and quality improvement (Figure 3). The study protocol was registered in the Clinicaltrials.Gov (NCT03920501). The study protocol follows the recommendations of the SPIRIT 2013 Statement (supplementary file 1).[27]

Intervention

Intervention group (Tele-ICU) (Table 3)

Trial intervention consists of:

1. *Daily multidisciplinary rounds* (DMR) *led by remote intensivists* - Discussions are conducted by an intensivist located in a remote centre (tele-intensivist) and the local

multidisciplinary team (doctor, nurse and physiotherapist). DMRs takes place from Monday to Friday, in predetermined hours (mostly during the mornings), using Telemedicine equipment, and approach every patient admitted to the participating ICUs. The main objective of DMR conducted by a tele-intensivist is to discuss diagnostic hypotheses, active problems and create a treatment plan until the next DMR. Tele-intensivists make recommendations based on updated scientific evidence, suitable to the local context. Clinical protocols in texts and videos 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 randomisation and establishment of a DMR routine. Electronic forms for patient follow-up serves as a guideline (Index) and are filled out by tele-intensivists. According to the current regulation (national resolution from the Brazilian Federal Council of Medicine, CFM Resolution 1643 of 2002), tele-intensivists does not act directly upon patients, but are rather mediated by the local team. Therefore, the local healthcare practitioners implement the treatment plan. Indicators of adherence to recommendations made by tele-intensivists are registered. Tele-intensivists do not write medical prescriptions, nor gives 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.

2. *Management of ICU performance* - The variables collected for the trial (table 1) are presented aggregately in reports available for each coordinator of the participating ICUs as well as for tele-intensivists. Data from Case Report Forms - CRFs (REDCap®,

Vanderbilt University Medical Center, TN, USA) are used to automatically feed dashboards in real-time, specially developed for this purpose (R Studio/Shiny®, Boston, MA, USA). In addition, 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 randomised 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, these data are not available for the care team nor to the coordination of the participating ICUs.

Sites

The list of potential units was retrieved from the national registry of health facilities ("Cadastro Nacional de Estabelecimentos de Saúde – CNES", in Portuguese), filtering those facilities with at least 8 ICU adult beds available.

Inclusion/Exclusion

The ICUs are invited by electronic means for an interview in which the eligibility and feasibility criteria below will be verified.

Inclusion criteria for ICUs

- ICUs of public or philanthropic hospitals
- ICUs with a minimum of 8 ICU beds

- ICUs with on-site registered doctors and nurses

Exclusion criteria for ICUs

- ICUs that already presented DMRs, defined as:

  - 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

  - Monthly management of indicators (audit and feedback) with specific planning.

- Specialized ICUs (ICUs admitting exclusively cardiac surgery, neurological, burned patients).
- Step-down units or coronary units

Patients

All consecutive patients that fulfil the inclusion criteria and none of the exclusion criteria will be enrolled.

Inclusion/Exclusion

The patients admitted in the ICU who currently meet the following inclusion criteria are included:

- Age ≥18 years old
- Patients admitted to the ICU after the beginning of the trial

Exclusion criteria for patients

- Patients admitted to the ICU due to justice-related issues (since in such circumstances the ICU admission or discharge may be determined by law and not medical reasons)
- Patients previously included in the TELESCOPE trial (for the analysis of the primary outcome).

Randomisation

The 30 ICUs are randomly assigned to either the intervention group (n=15) or the control group (n=15) using a restricted randomisation algorithm that minimizes imbalance between treatment groups across the following baseline covariates at the ICU level: number of ICU beds, mean SAPS 3, mean ICU length of stay (LOS), the standardized mortality rate (SMR), the standardized resource use (SRU), and a dummy indicator for Brazilian region where the ICU is located (South/Southeast x North/Northeast/Central-West).[28 29] The randomisation unit will be the ICU to avoid contamination of the intervention. Only one ICU per hospital will be included in the trial. The randomisation is performed at three times, including 14 units during the first randomization, followed by 7 and 9 units. 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.[28] To ensure allocation concealment, the statistician responsible for the randomisation list receives only the ICU identifier code, being unaware of which unit it refers to. The allocation list is sent to the study coordinator, who informs the ICUs about the randomisation. The allocation will be maintained until the end of the study.

Blinding

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 of the DMRs and monthly feedback/audit meetings.

Follow-up

Patients are followed up until hospital discharge by the health care worker responsible for data collection.

Outcomes

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 time of transfer to another care facility or another hospital, 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.

Secondary exploratory outcomes

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

- Classification of the unit according to the profiles defined by the SRU and the SMR.[30] The SRU reflects the observed / expected rate of resources used (estimated as ICU length of stay for surviving patients), adjusted by patient's severity of illness.[31 32] 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 four groups: "most efficient" (SMR and SRU < median); "least efficient" (SMR, SRU > median); "overachieving" (low SMR, high SRU), "underachieving" (high SMR, low SRU)[31]

- In-hospital mortality, defined as death by any cause from date of ICU admission until the date of hospital discharge or death, whichever comes first
- Incidence of central line-associated bloodstream infection (CLABSI), as defined by the CDC[33]
- Incidence of ventilator-associated event (VAE), as defined by the CDC[34]
- Incidence of catheter-associated urinary tract infection (CAUTI), as defined by the CDC[35]
- 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
- Patient-days receiving oral or enteral feeding, defined as any amount oral or enteral diet
- Patient-days under light sedation or alert and calm [Richmond Agitation-Sedation Scale (RASS) = -3 to +1]
- Rate of patients under normoxaemia [peripheral oxygen saturation (SpO_2) between 92% and 96%]

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
- Compliance to head of bed elevation for patient under MV
- Rate of central venous catheter (CVC) use and duration
- Rate of urinary catheter use and duration
- Adequate prevention of venous thromboembolism (VTE)
- Rate of patients with adequate glycaemic control

We will truncate the primary and secondary outcomes follow-up at 90 days.

Data collection

At the patient level, the following data is collected (Table 4):

At the time of ICU admission:

- Identifier, date of birth, gender, main reason of ICU admission (adapted from APACHE III),[36] readmission status
- Anthropometric characteristics, comorbidities (adapted from SAPS3),[37] functional status (adapted from ECOG)[37]
- Respiratory, cardiovascular, and renal support
- Diet and sedation status

- Presence of devices: central venous catheter, arterial line, permanent catheters, urinary catheter, oro/naso-tracheal catheter and traqueostomy
- Date and time of hospital admission
- Date and time of ICU admission
- Simplified Acute Physiology (SAPS 3) score[32]
- Sequential organ failure assessment (SOFA) score[38 39]

Throughout the ICU admission:

- Documented goals from the DMR
- Documented discharge order status, defined as any mention to readiness to discharge or ICU transference order
- MV status and mechanical ventilation parameters
- SpO_2 range for patients on oxygen therapy
- Head of bed elevation for patients under MV
- Spontaneous respiratory test, accidental extubation or re-intubation events
- Need of vasoactive drugs and renal replacement therapy
- Continuous sedative infusion and light sedation strategy (reduction/daily interruption)
- Daily value (categorized below, above or within -3 to +1 range) of the RASS for patients undergoing continuous sedation at a predetermined time
- Adequacy of VTE prophylaxis: considered adequate when patient is bedridden without any of the following exclusion criteria: active bleeding, stress gastric ulcer, uncontrolled arterial hypertension (>180/110 mmHg), coagulation disorder, allergy,

kidney failure (Cl<30 ml/min), ocular or cranial surgery in last 2 weeks, and lumbar puncture in last 24h).

- Presence of oral or enteral nutrition
- Glycemic control: considered adequate if between 60 to 180 mg/dL
- Notification of health-care-related infection episodes according to CDC (Centers for Disease Control and Prevention) criteria:
    - Central-line associated bloodstream infection (CLABSI)[33]
    - Ventilator-associated events (VAE)[34]
    - Catheter-associated urinary tract infection (CAUTI)[35]
    - Date and time of central venous catheter (CVC) insertion for patients undergoing CVC insertion
- Date and time of withdrawal of CVC for patients undergoing CVC insertion
- Date and time of indwelling urinary catheter (IUC) insertion for patients submitted to IUC insertion
- Date and time of withdrawal of IUC for patients undergoing IUC insertion
- Documentation of decisions for limiting the life support considering any mention to withholding or withdrawing in the medical records

At the time of ICU discharge

- Date and time of ICU discharge
- ICU outcome: discharge to ward, hospital transfer, death

At the time of hospital discharge

- Date and time of hospital discharge

- Hospital outcome: hospital transfer, death

Data collection and management

Trained health care workers collect data, without any involvement from the study committees and investigators. We developed a standard CRFs for the trial, with extensive validation and piloting aiming clarity and consistency.

Data is input 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. Medical data from tele-intensivist consultations is generated and stored using a specific platform developed by the Tele-ICU Department of the Hospital Israelita Albert Einstein/São Paulo - Brazil. Images and audio are never saved or stored. The electronic files are stored in the hospital's servers in a controlled and secure environment to guarantee confidentiality. Furthermore, access to all documents is user and password controlled. To ensure data quality, the following procedures are performed:

- All professionals responsible for data collection are trained before the beginning of the trial in order to guarantee clear definitions for accurate data collection;
- A research nurse from the Coordinating Centre is available 24/7 to solve any problem and question about data collection;
- Data input in the system are submitted to near real-time verifications to detect missing data, values outside expected and logic patterns;
- Remote data monitoring is performed regularly to detect patterns of anomalies, consistency or credibility problems and other anomalies – according to pre-established queries created by the system. Any missing data or outlier is individually reviewed for inspection;

- The Coordinating Centre reviews follow-up reports regularly to ensure their consistency and completeness;
- Centre monitoring is performed while the study is being conducted. A trained professional is assigned by the Coordinating Centre to monitor the study participating centres. All the information obtained during the monitoring visits are strictly confidential.

Monitoring

Interim analyses

Since our intervention gathers the best available evidence for care of critically ill patients admitted to the ICUs, and we do not predict inherent risks in the performance of the trial, interim analyses are not planned. Therefore, a formal Data Monitoring Committee was deemed unneeded. Adverse events are not expected to occur but could be reported by local researchers, data assistants, and local doctors.

Intervention Monitoring

Considering the study aim is to evaluate the impact of a complex intervention (composed by DMR, management of ICU performance indicators, and provision of clinical protocols), specific data (implementation indicators) will be collected and followed in order to ensure adherence to the protocol:

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 to study team monthly reports 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.

Auditing

Trial conduct is subjected to audit by Einstein Research Integrity Committee, at any time, independently of the IRB and research team, the same way as any interventional studies performed at Albert Einstein Hospital (random selection).

Power/Sample size calculation

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".[40] Using data from 20 ICUs (10 ICUs from Ranzani et al,[41] 10 ICUs from the ORCHESTRA study,[42] available in the *ems* R package), we estimated an intraclass correlation coefficient 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. If we use a coefficient of variation of cluster size, estimated by the expected minimum and maximum method, we will maintain 80% power if the difference between the clusters minimum and maximum size is 150 patients. If needed, after the baseline period, we

might review the sample calculation and simulate the power for secondary outcomes, using the data from the selected ICUs.

Analysis

All analyses will be thoroughly described in a statistical analysis plan (SAP), which will be concluded and submitted for publishing prior to database closure and the beginning of analyses. Primary statistical analyses will be performed according to the intention-to-treat principle. All outcomes at the patient-level will be performed using models that account for correlated data within each ICU (ie, ICU as a cluster) with generalised linear mixed models and adjusted by pre-specified covariates, as will be specified in the SAP. Pre-specified secondary outcomes and subgroup analyses will not be adjusted for multiple comparisons. They should, therefore, be interpreted as exploratory. We pre-specified three subgroups: type of admission (medical vs. surgical), by tertiles of SAPS3 and mechanical ventilation status (invasive MV vs. not-invasive MV). Sub-groups will be analyzed as an interaction term.

We will evaluate the calibration of the SAPS3 model with data from the baseline period. If necessary, we will recalibrate the model for the studied population. We plan to perform multiple imputation if missing data on core variables will be >5% and we will use standard steps for multiple imputation using chained equations. All analyses will be performed with program R (3.4.1 version, the version will be updated at the time of analysis).

ETHICS AND DISSEMINATION

The project was approved by local Research Ethics Committee (IRB) of the coordinating study centre (Hospital Israelita Albert Einstein) (CAAE: 01523118.0.1001.0071) and by the local IRB from each one of the 30 ICUs (supplementary file 2), following the Brazilian legislation. A specialist in regulatory process will oversee and support the local

process. Any modifications in the protocol that might affect the development of the study and its potential benefits or safety, including changes in the objectives, design, study population, sample size, interventions or relevant management aspects, will require amendments to the protocol. Such amendments should be submitted to the IRB of the coordinating centre and all the IRBs at the participating centre for proper approval. There will be rigorous procedures of protocol version control.

The need for patients' written informed consent was waived in all 30 centres. For one centre, it was requested written informed consent for health care professionals involved in the tele-ICU visits. We obtained written agreement from the Director of each institution as well as by the ICU coordinator.[43-46]

Therefore, the set interventions are not specifically directed to the patients but to the whole cluster together: the ICU (intervention type A).[47] In this type of interventions, there is only one decision to be made for each cluster and individual choice are not appropriated.[47] In this sense, informed consent was proposed and signed in the cluster-level. In the best interest of patients, medical teams and other professionals, the Hospital Director and the Head of ICU (Physician) were the responsible to sign the consent form. This proposal was approved by all the involved IRBs (coordinating centre and the IRBs of each one of the 30 participant hospitals).

All the information in the study will be stored (in paper and/or magnetic media) at the coordinating centre. All patient-level data will be anonymized, and will be accessed only by the data manager and statistician. Access to information from the participants (during the visits) will be restricted to the intensivists performing daily rounds via Telemedicine. All records with names or other identifiers will be stored separately from the study records. Information on patients will not be disclosed except for regulatory purposes.

The TELESCOPE study Steering Committee commits to publishing the study results, whatever they may be. The results of this study will be mainly disseminated through international scientific publication. The main result of this project will be reported in an article and sub-studies are planned. Results of this project are expected to be presented in major sessions at national and international congresses, especially in the field of intensive care medicine. Study results are expected to be promoted to the lay press and disseminated in various media outlets due to its impact on the health system.

TRIAL STATUS

This paper presents the protocol for the TELESCOPE trial (original version, 1.0, approved in 07/11/2018). The baseline period started on 01/06/2019. First randomisation and interventions started in 05/08/2019. At the time of first version of the manuscript submission, data collection for the trial was ongoing and due to be complete in the first semester of 2021.

ADDITIONAL INFORMATION

Funding

The study was conducted in partnership with the Brazilian Ministry of Health through the Institutional Development Program of the Unified Health System (PROADI - SUS, NUP 25000.018804/2018-23.), and classified in one of the objectives of the National Health Plan, highlighting the relevance and potential contribution of the project to the governance of the SUS, according to the ordinance 3.362, 12/8/2017.

Authorship

Authorship will follow current guidelines of International Committee of Medical Journal Editors (ICMJE). Executive and Steering Committee are planned to be list as authors/co-authors, since fulfilling authorship criteria (substantive contributions to the design, conduct, interpretation, and reporting of a clinical trial). If some protocol authors are not named author info publications (not fulfil such criteria), their names will be acknowledged in the reports. Three main papers are planned: Protocol paper, Statistical Analysis Plan, Main Paper (trial results). Principal Investigator - AJP, Senior Researcher - DTN and OTR - Statistician Specialist will share and alternate in first, second and last positions. Local PIs will be cited as collaborators in the main paper. The same is planned for abstracts or oral presentations in international meetings. Disputes regarding authorship will be settled by the Study Chair and Executive Committee. Professional writer's participations are not planned.

Competing interests

None declared.

Patient consent

Not required.

Patient and public involvement

This research was done without patient involvement in its design or development. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. This was due to logistic limitations (critical care patients in a national wide study). Outcomes were chosen according to traditional indicators in the critical care area.

Ethics approval

This study will be conducted according to the resolution no 466/12 of the Brazilian National Health Council (http://bvsms.saude.gov.br/bvs/saudelegis/cns/2013/res0466_12_12_2012.html). The study protocol has been approved by the Research Ethics Committee of the coordinating site (approval number: CAAE 01523118.0.1001.0071) and the Research Ethics Committees of all participant institutions (supplementary file 2).

Acknowledgments

The authors would like to thank the central TELESCOPE team, data collection team of each participating ICU, as well as the Hospital Israelita Albert Einstein, the Brazilian Ministry of Health, and the Brazilian Research in Intensive Care Network (BRICNET) for their support in conducting the study.

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Table 1. Synopsis (WHO trial registration data set)

Data category	Information
Primary register and identification number	ClinicalTrials.gov - NCT03920501
Date of first registration	April 19, 2019
Secondary identification numbers	PROADI 25000.018804/2018-23
Development agency / funding source	Ministry of Health (Institutional Development Program of the Unified Health System – PROADI SUS)
Primary sponsor	Ministry of Health
Secondary sponsor	Hospital Israelita Albert Einstein
General contact	*DN*, MD, PhD. Phone: (+55) 11 96490-7494, e-mail: danilo.noritomi@einstein.br
Academic contact	*DN*, MD, PhD. Phone: (+55) 11 96490-7494, e-mail: danilo.noritomi@einstein.br
Public title	The influence of Telemedicine in the treatment of Intensive Care Unit (ICU) patients.
Academic title	Multicentric, controlled, cluster randomized superiority study to evaluate the effectiveness of specialist assistance via Telemedicine in patients admitted to ICUs in Brazilian hospitals.
Countries involved in recruitment	Brazil
Health conditions/ problems studied	ICU care design, critically ill patients, Telemedicine.
Interventions	Comparator: use of Telemedicine (intensivists) in daily ICU multidisciplinary rounds and quality indicators management (audit and feedback) Control: ICUs in the same strata, with no intervention

Data category	Information
Main inclusion and exclusion criteria	ICU clusters (all adult patients admitted after the beginning of the study will be included, with the exception of those admitted for non-medical reasons) Age: ≥ 18 years old Sex: Both Accepts volunteers: No Inclusion criteria for units: Public Hospital ICUs with a minimum of 8 hospital beds interested and committed to participating in the study. Exclusion criteria for units: Units with fully established daily multidisciplinary rounds by an intensivist, specialized units (such as ICUs admitting exclusively cardiac surgical or neurological patients) or step-down units.
Type of study	Intervention / cluster Allocation: randomization stratified by patients' previous ICU length of stay Intervention design: parallel assignment Masking: Open Primary purpose: Quality improvement
Expected date of first inclusion	February 2019
Sample size	30 clusters (15 in each group), approximately 15.000 patients
Recruitment status	Not initiated (expected for 2019)
Primary outcome	Length of stay in the ICU (days)

Data category	Information
Secondary outcomes	• Classification based on the association between standardized mortality ratio (SMR) and standardized resource use (SRU) • Rate per patient per day receiving oral or enteral nutrition • Rate per patient per day in appropriate sedation (RASS = -3 to +1) • Rate of normoxic patients on oxygen therapy (92% ≥SpO2≥96%) • Time without mechanical ventilation (MV) in 28 days • Duration of CVC use • Duration of vesical delayed probe (VDP) use • Incidence of central line-associated bloodstream infection (CLABSI) (43) • Incidence of ventilator-associated pneumonia (VAP) (44) • Incidence of catheter-associated urinary tract infection (CAUTI) (45) • Hospital Mortality

Table 2. Project version control

Date	Comments
September 25, 2018	Original version (version 1.0)
October 09, 2020	Updated risks and benefits (version 2.0)
December 31, 2020	Enrolment period extension (version 3.0)

Table 3. Intervention framework

Component	Frequency	Tool	Goal	Attendees
Multidisciplinary rounds (DMR) by telemedicine	Daily (Monday – Friday)	Semi – structured patient electronic forms	Establish a therapeutic plan for each ICU patient	Bedside clinicians, nurse and physiotherapists
Discussion of care performance indicators performed through virtual meetings	Monthly	Report with quality indicators (monthly temporal series)	Action Plan for suboptimal quality indicators	Bedside clinicians, ICU head of department, quality improvement members

Table 4. Patient data collection schedule

	Baseline period			After randomisation		
	Admission	Daily	Discharge	Admission	Daily	Discharge
Patient details	x			x		
Pre ICU events	x			x		
Type and cause of admission	x			x		
Severity scores (SAPS 3 and SOFA)	x			x		
Comorbidities / functional status	x			x		
Treatment goals		x			x	
Organ support and devices	x	x		x	x	
Hospital-acquired infections		x			x	
Length of stay (ICU/Hospital)		x	x		x	x
Mortality and destination (ICU/Hospital)		x	x		x	x

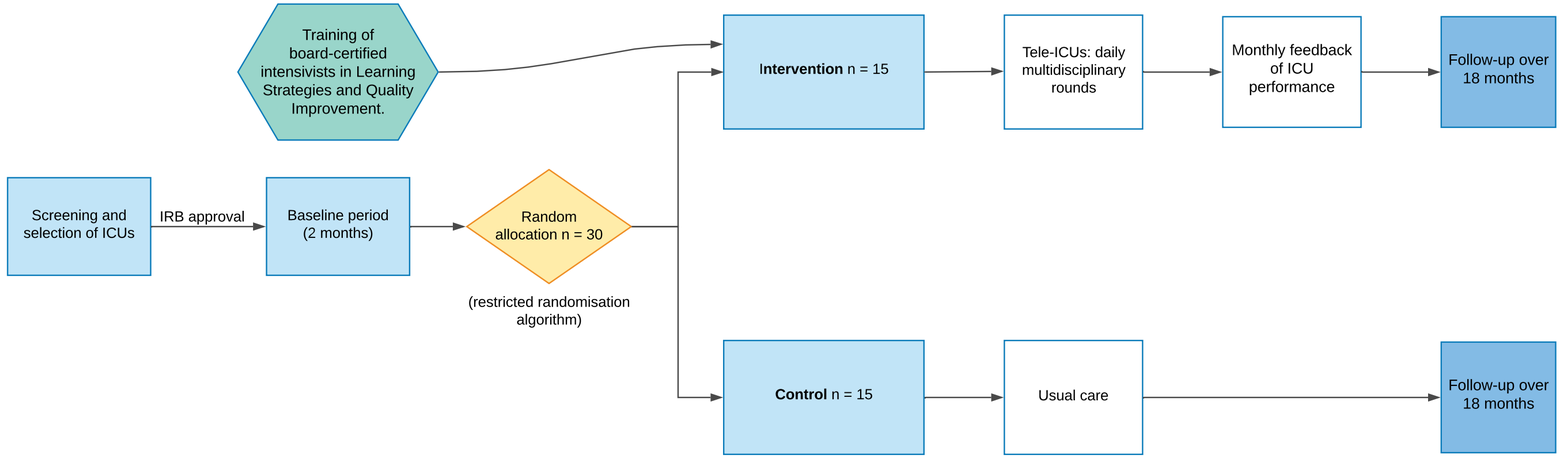
ICU: intensive care unit; SAPS 3 score: simplified acute physiology score; SOFA score: sequential organ failure assessment score.

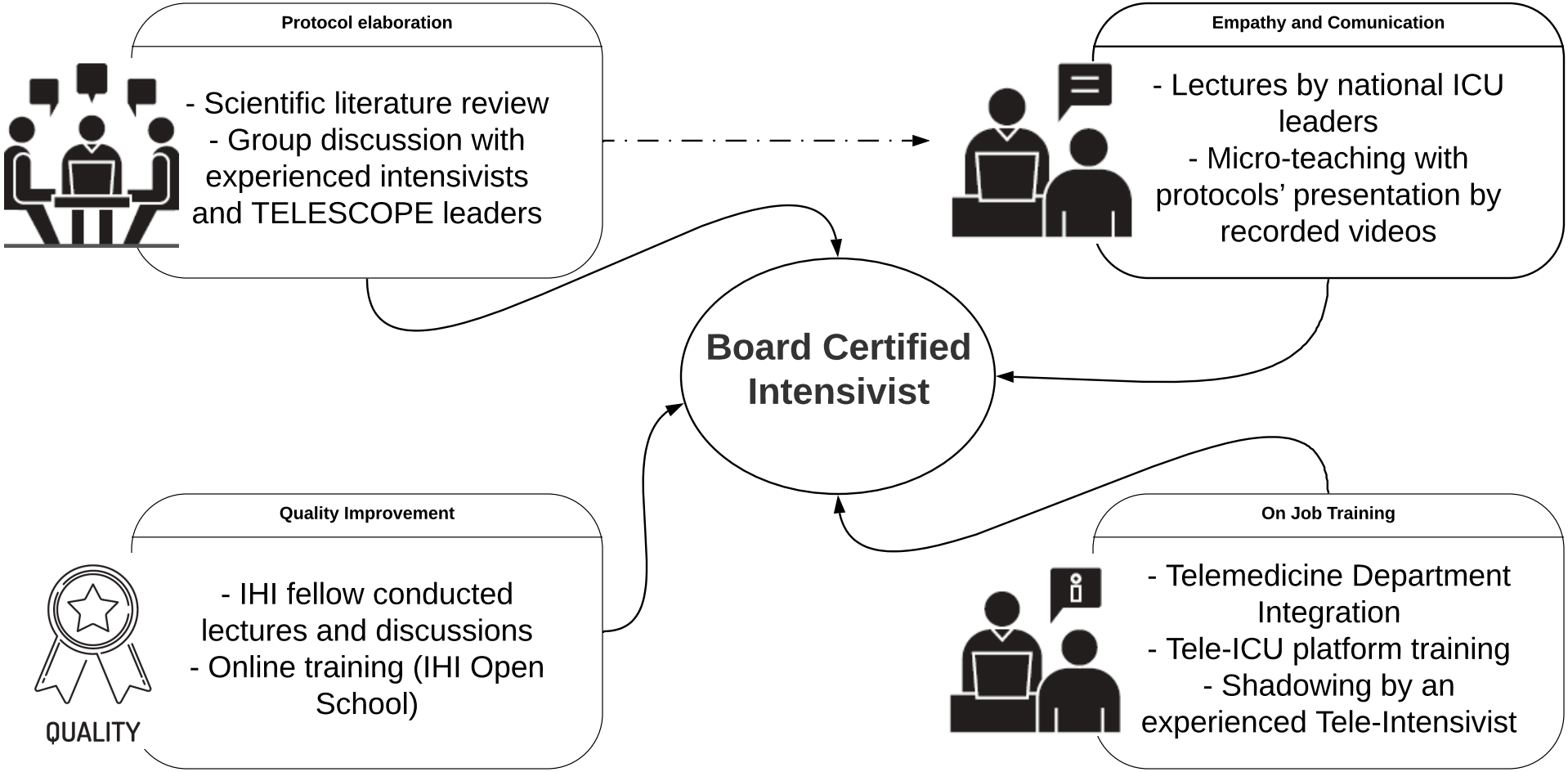
FIGURES

Figure 1. Geographic distribution of the 30 ICUs participating in the TELESCOPE trial

Figure 2. Trial timeline, randomisation, intervention and follow-up
ICU: intensive care unit; IRB: institutional review board

Figure 3. Illustration of the multicomponent training of board-certified intensivists to act in the intervention arm
ICU: intensive care unit; IHI: Institute for Healthcare Improvement


Training of board-certified intensivists in Learning Strategies and Quality Improvement.
Intervention n = 15
Tele-ICUs: daily multidisciplinary rounds
Monthly feedback of ICU performance
Follow-up over 18 months
Screening and selection of ICUs
IRB approval
Baseline period (2 months)
Random allocation n = 30
(restricted randomisation algorithm)
Control n = 15
Usual care
Follow-up over 18 months


Protocol elaboration
- Scientific literature review
- Group discussion with experienced intensivists and TELESCOPE leaders
Empathy and Comunication
- Lectures by national ICU leaders
- Micro-teaching with protocols' presentation by recorded videos
Board Certified Intensivist
Quality Improvement
QUALITY
- IHI fellow conducted lectures and discussions
- Online training (IHI Open School)
On Job Training
- Telemedicine Department Integration
- Tele-ICU platform training
- Shadowing by an experienced Tele-Intensivist

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	01
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	01
	2b	All items from the World Health Organization Trial Registration Data Set	02-04
Protocol version	3	Date and version identifier	01 and 05
Funding	4	Sources and types of financial, material, and other support	01
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	01
	5b	Name and contact information for the trial sponsor	01
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	06
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	07-10

Based in the file "2. TELESCOPE_protocol_BMJopen_manuscript resubmission clean copy.docx"

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	13-14
	6b	Explanation for choice of comparators	15-17
Objectives	7	Specific objectives or hypotheses	14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	14-15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14-15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17-18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-16
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	25-26
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	18
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	19-21

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15 (Figure 2)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	26
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18-19
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	18-19
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	19
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	19
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	19
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	21-24

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	24-25
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	24-25
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	26-27
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	26
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	26
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	25
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	25
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	25
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	26
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	27-28

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	27-28
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	27-28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	28
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	29
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	28
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	28
	31b	Authorship eligibility guidelines and any intended use of professional writers	28
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary File 2. Research ethics committees of the TELESCOPE trial.

Centre	HOSPITAL (Brazilian estate)	RESEARCH ETHICS COMMITTEE	APPROVAL NUMBER
Coordinator	Hospital Albert Einstein (SP)	Hospita Israelita Albert Einstein HIAE	CAAE 01523118.0.1001.0071
Centre 1	Hospital Universitário da Universidade Federal de Sergipe (SE)	Universidade Federal de Sergipe UFS	CAAE 01523118.0.2005.5546
Centre 2	Hospital Municipal Senhora Santana (Hospital Microrregional) (MG)	Faculdade de Talentos Humanos - FACTHUS	CAAE 01523118.0.2001.9028
Centre 3	Santa Casa de Paranavaí (PR)	Universidade Estadual do Parana UNESPAR	CAAE 01523118.0.2025.9247
Centre 4	Hospital de Caridade de Irati (PR)	Universidade Estadual do Centro Oeste - Campus de Irati - UNICENTRO	CAAE 01523118.0.2015.8967
Centre 5	Hospital Regional de Gurupi (TO)	Centro Universitario UNIRG	CAAE 01523118.0.2026.5518
Centre 6	Hospital Nossa Senhora da Oliveira – HNSO (RS)	Comitê de Ética em Pesquisa do Hospital Nossa Senhora de Pompéia	CAAE 01523118.0.2023.5331
Centre 7	Hospital de Trauma Dom Luiz Gonzaga Fernandes (PB)	Secretaria de Saude do Estado da Paraíba	CAAE 01523118.0.2033.5186
Centre 8	Hospital Regional de Assis (SP)	Hospital Regional do Câncer de Presidente Prudente HRCPP	CAAE 01523118.0.2012.8247
Centre 9	Hospital Municipal de Paracatu (MG)	Faculdade deeCiências e Educação Sena Aires	CAAE 01523118.0.2010.5595
Centre 10	Hospital Regional Dr. Clodolfo Rodrigues de Melo (AL)	Universidade Federal de Alagoas	CAAE 01523118.0.2029.5013
Centre 11	Hospital Municipal Rocha Faria (RJ)	Secretaria Municipal de Saúde do Rio de Janeiro - SMS/RJ	CAAE 01523118.0.2021.5279
Centre 12	Hospital Universitario Nova Esperança (PB)	Escola de Enfermagem Nova Esperança LTDA	CAAE 01523118.0.2013.5179
Centre 13	Santa Casa de Itapetininga (SP)	Faculdade de Ciências Médicas e da Saúde da Pontifícia Universidade Católica de São Paulo - FCMS-PUC/SP	CAAE 1523118.0.2038.5373
Centre 14	Casa de Caridade de Muriaé - Hospital São Paulo (MG)	Hospital Santa Paula - SP	CAAE 01523118.0.2036.5670
Centre 15	Santa Casa de Misericórdia de Votuporanga (SP)	CEP UNIFEV	CAAE 01523118.0.2006.0078
Centre 16	Irmandade da Santa Casa de Sorocaba (SP)	Universidade de Sorocaba UNISO	CAAE 01523118.0.2022.5500
Centre 17	Santa Casa de Misericórdia de Belo Horizonte (MG)	Santa Casa de Misericórdia de Belo Horizonte - SCMBH	CAAE 01523118.0.2008.5138
Centre 18	Hospital da Restauração - Secretaria Estadual de Saúde (PE)	Hospital da Restauração - PE CEP/HUOC/PROCAPE	CAAE 01523118.0.2004.5198
Centre 19	Hospital Geral de Roraima (RR)	Universidade Federal de Roraima - UFRR	CAAE 01523118.0.2011.5302
Centre 20	Hospital Geral de Vitória da Conquista (BA)	Secretaria da Saude do Estado da Bahia - SESAB	CAAE 01523118.0.2009.0052
Centre 21	Hospital Regional Justino Luz (PI)	Hospital Universitário da Universidade Federal do Piauí UFPI	CAAE 01523118.0.2030.8050

Centre 22	Complexo Hospitalar Mangabeira Governador Tarcísio Burity (PB)	UFPB - Centro de Ciências da Saúde da Universidade Federal da Paraíba UFPB	CAAE 01523118.0.2003.5188
Centre 23	Hospital Regional de Barbacena Dr. José Américo (MG)	Fundação Hospitalar do Estado de Minas Gerais FHEMIG	CAAE 01523118.0.2024.5119
Centre 24	Hospital Geral de Promissão Prefeito Miguel Martin Gualda (SP)	Hospital Regional do Câncer de Presidente Prudente HRCPP	CAAE 01523118.0.2037.8247
Centre 25	Hospital Maternidade e Pronto Socorro Santa Lúcia LTDA (MG)	Hospital Vera Cruz HVC/ MG	CAAE 01523118.0.2002.5135
Centre 26	Hospital Municipal Padre Germano Lauck - Hospital Municipal de Foz do Iguaçu (PR)	Centro Universitário Dinânica das Cataratas UDC	CAAE 01523118.0.2007.8527
Centre 27	Santa Casa de Anápolis (GO)	UEG - Universidade Estadual de Goiás	CAAE 01523118.0.2031.8113
Centre 28	Santa Casa de Misericordia de Passos (MG)	Santa Casa de Misericordia de Passos SCMP	CAAE 01523118.0.2014.8043
Centre 29	Hospital Geral e Maternidade Tereza Ramos (SC)	Secretaria de Estado da Saúde de Santa Catarina/SES	CAAE 01523118.0.2016.0115
Centre 30	Hospital Regional do Paranoá (DF)	Comitê de Ética em Pesquisa FEPECS/SES-DF	CAAE 01523118.0.2019.5553