PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	TELE-critical care verSus usual Care On ICU PErformance (TELESCOPE): protocol for a cluster-randomised clinical trial on adult general ICUs in Brazil
AUTHORS	Noritomi, Danilo; Ranzani, Otavio; Ferraz, Leonardo; dos Santos, Maura; Cordioli, Eduardo; Albaladejo, Renata; Serpa Neto, Ary; Correa, Thiago; Berwanger, Otávio; de Morais, Lubia; Schettino, Guilherme; Cavalcanti, Alexandre; Rosa, Regis Goulart; Biondi, Rodrigo; Salluh, Jorge; Azevedo, Luciano Cesar; Pereira, Adriano

VERSION 1 – REVIEW

REVIEWER	Pedja Kovacevic University Clinical Centre of Republika Srpska, Bosnia and Herzegovina
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	In this catastrophic period of time Tele critical care will be very helpful for developing countries as well as in high income countries.

REVIEWER	Lisa-Mae Williams Baptist Health South Florida, USA
REVIEW RETURNED	01-Sep-2020

GENERAL COMMENTS	Abstract - does not clearly state the research question. Although methods are described the research question is needed for the reader to quickly identify the studies purpose Page 7, Line 19 - Please reword or remove "aiming a scalable intervention" - the meaning is unclear Page 7, Line 36 - period not a comma at end of this bullet point Page 8, Line 28 - please provide a reference for first sentence Page 8, Lines 45 - 50 - Need to define telecommunication versus telemedicine - these are not interchangeable terms Page 10 Line 35 - keep font consistent tele-ICU or TELE-ICU Page 10 - regarding the Intervention group: most tele-ICU models have the tele-intensivists prescribing medication and giving orders. Seems there needs to be a 3rd trial arm in which tele-intensivists are modeling the standard approach for tele-intensivists interventions. Otherwise this is a significant limitation of this proposed trial

	Page 10, Line 50 - Tele-UTI? Page 12, Line 23-25 - what does "indicators" refer to? Page 12, line 60 - what level of training is required for the on-site doctors. Are these open or closed ICUs? Page 18, lines 33 and 38 - what standards or evidence based protocols will be used to measure compliance Recommend reading - Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. JAMA. 2011;305(21):2175-2183. doi:10.1001/jama.2011.697

REVIEWER	Chantal Mérette CERVO Research Center Laval University Québec City, Province of Québec, Canada
REVIEW RETURNED	28-Nov-2020

GENERAL COMMENTS	A better description of the restricted randomisation is needed. The use of blocks will allow to assign exactly 15 ICUs to the intervention group but this will not help to achieve a better balance of the known confounders. Potential confounders should first be acknowledged (e.g. number of ICU beds, or any characteristics of the ICU collected at baseline that could impact the outcomes) and taken into accounted in a stratification approach as part of the restricted randomisation.

REVIEWER	Margaret Stedman Stanford University United States
REVIEW RETURNED	02-Dec-2020

GENERAL COMMENTS	1) data collection is close to complete, ending in December 2020 and this may be a concern for the journal. 2) Please include how the randomization blocks were defined, by what variables. 3) Please describe the time period for collecting the secondary exploratory outcomes. 4) Please include a plan for handling missing data. 5)What distribution will be assumed for the analysis of the ICU stay outcome?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Pedja Kovacevic

Comments to the Author
In this catastrophic period of time Tele critical care will be very helpful for developing countries as well as in high income countries.
ANSWER: Thank you very much for your comment. We strongly believe our results will help the

decision making in this important field.

Reviewer: 2 Lisa-Mae Williams

Comments to the Author
Abstract does not clearly state the research question. Although methods are described the research question is needed for the reader to quickly identify the studies purpose
ANSWER: Thank you very much. We realized that the aim of the study was not stated in the original version. The new version of the manuscript corrects this.

Page 7, Line 19 - Please reword or remove "aiming a scalable intervention" - the meaning is unclear
ANSWER: We removed that. We intended to say it could be reproduced in a different setting since the steps were documented, but we believe this is not an objective finding

Page 7, Line 36 - period not a comma at end of this bullet point
Response: Thank you for your observation, we corrected it

Page 8, Line 28 - please provide a reference for first sentence
ANSWER: We have provided 3 references for thar sentence

Page 8, Lines 45 - 50 - Need to define telecommunication versus telemedicine - these are not interchangeable terms
ANSWER: Thank you very much for your careful observation. Even though several definitions of Telemedicine exist, the most consensuses ones contemplate the remote practice of medicine using two-way voice AND visual communication. For such reason we reframed our sentence in the new version of the manuscript:
“Telecommunication use for health care practice, one of the components of Telemedicine, has been described since the advent of telecommunication.”

Page 10 Line 35 - keep font consistent tele-ICU or TELE-ICU
ANSWER: Thank you for your observation, we corrected it

Page 10 - regarding the Intervention group: most tele-ICU models have the tele-intensivists prescribing medication and giving orders. Seems there needs to be a 3rd trial arm in which tele-intensivists are modeling the standard approach for tele-intensivists interventions. Otherwise this is a significant limitation of this proposed trial
ANSWER: As stated in our manuscript we have legal restrictions for remote prescribing medications and orders in Brazil. Such scenario did not change significantly even during the COVID-19 pandemic in our country: a local physician is still required to validate remote suggestions. In fact, we believe this is a strength point of Telescope trial, since it tests the delivery of a compartmental complex tool, i.e., the possibility of influencing others behavior in a remote fashion. This will bring an original information specially useful for countries with legal barriers such as ours.

Page 10, Line 50 - Tele-UTI?
ANSWER: Thank you for your observation, we corrected it : tele-ICU

Page 12, Line 23-25 - what does "indicators" refer to?
ANSWER:: Thank you for your observation, we corrected it : data

Page 12, line 60 - what level of training is required for the on-site doctors. Are these open or closed

ICUs?
ANSWER: We have added the word registered doctors (and nurses). There is no specific legislation in Brazil to work as a physician in ICU, except for being a physician with a regular register in the regional section of the Brazilian Medical Counsel (CRM). Nevertheless, there is a legal requirement for the ICU coordinator to be board-certified as an intensivist. Additional requirements, when they exist, are under the discretion of each hospital and are quite heterogeneous over Brazil

Page 18, lines 33 and 38 - what standards or evidence based protocols will be used to measure compliance
Recommend reading - Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. JAMA. 2011;305(21):2175-2183. doi:10.1001/jama.2011.697
ANSWER (inserted in the new version of the manuscript):
· 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).
· Glycaemic control: considered adequate if between 60 to 180 mg/dL

Reviewer 3. Chantal Mérette

Comments to the Author
A better description of the restricted randomisation is needed. The use of blocks will allow to assign exactly 15 ICUs to the intervention group but this will not help to achieve a better balance of the known confounders.
Potential confounders should first be acknowledged (e.g. number of ICU beds, or any characteristics of the ICU collected at baseline that could impact the outcomes) and taken into accounted in a stratification approach as part of the restricted randomisation.

ANSWER: Thank you for the opportunity to clarify this point. We used the algorithm for restricted randomization for cluster trials as described by Carter and Hood. We took account 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). We added this information in the protocol paper as below. We would like to highlight that all analyses will be thoroughly described in a detailed statistical analysis plan (SAP), which will be concluded and submitted for publishing prior to database closure and the beginning of analyses.
“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 ate 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.”
Carter BR, Hood K. Balance algorithm for cluster randomized trials. BMC Med Res Methodol 2008;8:65. doi: 10.1186/1471-2288-8-65

Reviewer 4: Margaret Stedman

1) data collection is close to complete, ending in December 2020 and this may be a concern for the journal.

ANSWER: The collection period was extended to the first semester of 2021. We updated it on the current version.

2) Please include how the randomization blocks were defined, by what variables.
ANSWER: We used the algorithm for restricted randomization for cluster trials as described by Carter and Hood. We took account 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). We added this information in the protocol paper as below.
"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 ate 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."

3) Please describe the time period for collecting the secondary exploratory outcomes.
ANSWER: We will follow-up all patients until in-hospital outcome. For the primary and secondary outcomes, we will truncate the follow-up until 90 days after ICU admission. We add this information to the protocol paper.

4) Please include a plan for handling missing data.
ANSWER: We will not impute outcome variables and we expect minimal or no missing values for them because they occur during ICU admission. Regarding covariates at ICU admission, we are expecting a limited number of missing values because of the active monitoring. For commonly used severity ICU scores, we will use the normal value category when it was not collected for the main analysis or if there are more than 5% of missing values, we will use multiple imputation with chained equations, following standard guidelines, in a sensitivity analysis.

5)What distribution will be assumed for the analysis of the ICU stay outcome?
ANSWER: As defined by now, we will use a log-transformed ICU LOS variable in a linear mixed model.
All these definitions will be better described in the SAP paper.W
The statistical analysis plan (SAP) is under final internal revision and will be evaluated by an external committee. We would like to highlight that all analyses will be thoroughly described in a detailed statistical analysis plan (SAP), which will be concluded and submitted for publishing prior to database closure and the beginning of analyses.

VERSION 2 – REVIEW

REVIEWER	Stedman, Margaret Stanford, Medicine
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	The section on randomization is still not clear. The randomization blocks (sizes 14,7, and 9) should all be multiples of 2 to achieve a balance between the 2 treatment groups. Also the number of variables is so many, the combinations of them would likely produce multiple small blocks. I suggest simplifying the number of blocking variables to no more than 3 given that you have only 30 sites to randomize. Another minor point is that the abbreviations LOS, SMR, and SRU are introduced in the outcomes section

	which follows the randomization section, so that they should be spelled out rather than abbreviated. The authors have explained the time periods for collecting the results. The authors state that they will monitor for missing data but this is not a statistical plan such as multiple imputation,

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4
Dr. Margaret Stedman, Stanford

Comments to the Author:
The section on randomization is still not clear. The randomization blocks (sizes 14,7, and 9) should all be multiples of 2 to achieve a balance between the 2 treatment groups. Also the number of variables is so many, the combinations of them would likely produce multiple small blocks. I suggest simplifying the number of blocking variables to no more than 3 given that you have only 30 sites to randomize. Another minor point is that the abbreviations LOS, SMR, and SRU are introduced in the outcomes section which follows the randomization section, so that they should be spelled out rather than abbreviated.

ANSWER: We are sorry for not being clear. This trial was not randomized by blocks as usually done and the word “block” might have created confusion. We performed the algorithm for randomization using restricted randomization three times (which we labelled blocks in the previous version). We defined a priori to randomized the 30 ICUs in 3 occasions and the number of units randomized at each occasion was determined pragmatically, ie, upon ethical approval and completion of 2 months’ period baseline collection, respecting the minimum of eight units during first randomization and minimum of six on subsequent randomizations.[1] The 3 randomizations included 14 units on the first time, 7 on the second, and 9 units at the end. The restricted algorithm aims to minimize the imbalance between treatment groups across the 6 baseline covariates and not by direct blocking/stratification. The algorithm carries on the information on the previous randomization to the following ones, as minimization. [1] We clarified this point in the manuscript. We also correctly spelled the abbreviations in advance.

Changes
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.

The authors have explained the time periods for collecting the results.

ANSWER: Thanks.

The authors state that they will monitor for missing data but this is not a statistical plan such as multiple imputation,

ANSWER: We plan to perform multiple imputation using chained equations and follow the standard guidelines for imputation in trials if there were more than 5% of missing values in core variables. We will use the standard steps [2]: 1) Description of missingness pattern, 2) evaluation of assumptions and plausibility of missing at random (MAR), 3) preparation of dataset, 4) model specification for imputation accounting for the analysis model, including the outcome variable in the model and auxiliary variables; 5) The number of imputations will be guided by the fraction of missing information (FMI),[3] 6) We will use Rubin-rules to combine the multiple imputed datasets. The detailed description of the statistical analysis plan, including multiple imputation item, will be described on the statistical analysis plan article in a separate publication.

Changes:

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.

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.

1 Carter BR, Hood K. Balance algorithm for cluster randomized trials. BMC Med Res Methodol 2008;8:65. doi:10.1186/1471-2288-8-65
2 Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393–b2393. doi:10.1136/bmj.b2393
3 Madley-Dowd P, Hughes R, Tilling K, et al. The proportion of missing data should not be used to guide decisions on multiple imputation. Journal of Clinical Epidemiology 2019;110:63–73. doi:10.1016/j.jclinepi.2019.02.016