PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Restrictive use of Restraints and Delirium Duration in the Intensive Care Unit (R2D2-ICU): Protocol for a French Multicentre Parallel-group Open Label Randomized Controlled Trial
AUTHORS	Sonneville, Romain; Couffignal, Camille; Sigaud, Florian; Godard, Virginie; Audibert, Juliette; Contou, Damien; Celier, Adam; Djibre, Michel; Schmidt, Julien; Jaquet, Pierre; Mekontso Dessap, Armand; Bourel, Claire; Bellot, Romane; Roy, Carine; Lamara, Fariza; Essardy, Fatiha; Timsit, Jean-François; Cornic, Renaud; Bouadma, Lila

VERSION 1 – REVIEW

REVIEWER	Yang, Chun Chiba University
REVIEW RETURNED	08-Feb-2024

GENERAL COMMENTS	The design for the study is well organized. I hope the findings of the study could be published soon. I will suggest how to restrain the ICU patients well and reduce the incidence for delirium.

REVIEWER	Tan, Alai The Ohio State University College of Nursing
REVIEW RETURNED	14-Feb-2024

GENERAL COMMENTS	The proposed multicenter RCT is to test the effect of restrictive use of physical restraint (PR) in reducing duration of delirium/coma among ICU patients receiving invasive mechanical ventilation as compared to a systematic use. It addresses an important topic and has great potential to change PR practice in the ICU setting and improve patient outcomes. Overall, it is a well written. Below are a few methods related issues that need further clarification. Major Page 11, lines 33-54. Patients are the units of randomization. Most interventions aim at practice change will conduct cluster RCTs (e.g., ICUs as the units of randomization) to reduce contamination. Clinicians tend to treat patients in the same unit similarly. Is it realistic that ICU providers treat patients randomized to intervention with “restrictive use of PR” protocol will not carry over such practice to the rest of the patients (including those randomized to control)? Just “practice guidelines outlines in the protocol for each group…” does not appear adequate to minimizing the risk of contamination. Any protocol to reduce and evaluate cross-contamination? Minor

	Page 17, lines 8-17. Please specify randomization units, allocation ratio, and randomization methods within each stratum (e.g., permuted block randomization with varying block sizes?). Page 20-21, statistical analysis. 1) Since patients are nested within provider and centers, please specify methods to adjust for clustering. 2) there are a large number of secondary outcomes. Please specify approach to adjust for multiple testing and avoid inflated family-wise type-1 error.

REVIEWER	Walsh, Timothy The University of Edinburgh
REVIEW RETURNED	16-Feb-2024

GENERAL COMMENTS	This is a protocol for a trial which appears to be almost complete comparing two different approaches to physical restraint in the ICU. This is a topical and controversial topic, and use of restraint varies internationally between almost no use to almost routine use in ICUs. 1. Consent process (page 9. The protocol appears t state that the PI or a physician representing the investigator will make this decision. Can the authors clarify what legal ethical consent process governs this process? It says on page 13 that the relative will be 'informed' rather than provide consent or non-objection. There is further information on pages 20-21 but is not clear exactly how this process works. Perhaps a diagram explaining how the different consent stages and use of deferred versus relative consent works would be useful? 2. Consent for follow-up consent will be after regaining capacity (page 10). Again can the authors clarify what will be the case for patients who die or fail to regain capacity in terms of the legal basis for inclusion in the research? 3. On page 10 the protocol states criteria for removal of PR in relation to agitation due to delirium. Given there are other causes of agitation, for example pain, anxiety, drug withdrawal syndromes how will they manage agitation in this wider context? 4. In Box 2 it would be informative to include what the 'eligible to physical restraint prescription' means as part of the actual inclusion criteria. This does not seem to be included in the text either and could be subjective and a source of bias or variation? 5. Under outcomes there is quite extensive justification of each outcome. This might be better is the introduction or design section as it detracts from clarity about the actual outcomes being measured. There is also some repetition with the background/introduction. 6. On page 15 it may be useful to clarify how the sedation practice will be standardised, especially as agitation and delirium are likely to be closely linked to the practice of early light sedation either by titration by nurses and/or daily sedation holds/interruptions. There is description on page 16 of a number of aspects of care, but it could be clearer what is intended to be standardised across groups and sites. 7. Although I appreciate that this trial is already almost completed, the protocol does not describe any 'process evaluation', in other words how the authors will measure what actually happened in terms of following the protocol. There is a major expectation that staff will follow the two approaches being compared, with high chance of cross-over and/or deviation. It will be important to understand what the difference in use of restraint actually was in

	the trial, which may not be the same as the intended protocol. This is an important aspect of complex intervention trials.

VERSION 1 – AUTHOR RESPONSE

Comments from the Reviewers:
Reviewer: 1
Dr. Chun Yang, Chiba University
Comments to the Author:
The design for the study is well organized. I hope the findings of the study could be published soon. I will suggest how to restrain the ICU patients well and reduce the incidence for delirium.
Response: We thank reviewer #1 for his kind comment on our manuscript.

Reviewer: 2
Dr. Alai Tan, The Ohio State University College of Nursing
Comments to the Author:
The proposed multicenter RCT is to test the effect of restrictive use of physical restraint (PR) in reducing duration of delirium/coma among ICU patients receiving invasive mechanical ventilation as compared to a systematic use. It addresses an important topic and has great potential to change PR practice in the ICU setting and improve patient outcomes. Overall, it is a well written. Below are a few methods related issues that need further clarification.
Response: We thank reviewer #2 for his positive comments on our manuscript.

Major
Page 11, lines 33-54. Patients are the units of randomization. Most interventions aim at practice change will conduct cluster RCTs (e.g., ICUs as the units of randomization) to reduce contamination. Clinicians tend to treat patients in the same unit similarly. Is it realistic that ICU providers treat patients randomized to intervention with "restrictive use of PR" protocol will not carry over such practice to the rest of the patients (including those randomized to control)? Just "practice guidelines outlines in the protocol for each group…" does not appear adequate to minimizing the risk of contamination. Any protocol to reduce and evaluate cross-contamination?
Response: Thanks for this remark.
A cluster study could have been considered but would have required more centres and more patients. Cluster studies also carry a significant risk of empty cluster. Moreover, this type of study is subject to other biases, including selection bias since the randomization arm is known in advance by investigators. Consciously or unconsciously, this may influence the physician's decision to include or not a given patient and thus create selection bias and imbalance between randomization groups. Therefore, the interpretation of the results generated from cluster trials need to be cautiously interpreted at the patient level. In conclusion, we believe that a cluster design would have been much heavier to conduct in terms of logistics, cost and does not guarantee the absence of bias. In our study, an extensive monitoring performed at the patient level also allows a high quality of collected data with respect to adherence to intervention or control arm, and study endpoints.
We added the following information on data collection and management :
Change in revised manuscript (page 10):
"Comprehensive monitoring at the patient level will be conducted to ensure the acquisition of high-quality data regarding adherence to the intervention or control arm, as well as to assess potential cross-contamination."

Minor

Page 17, lines 8-17. Please specify randomization units, allocation ratio, and randomization methods within each stratum (e.g., permuted block randomization with varying block sizes?).

Response: Thank you for this suggestion. The process of randomization is now detailed in the revised version of the manuscript, sections Randomization and sequence generation and Allocation concealment.

Change in revised manuscript:

« Randomization and sequence generation

The randomisation sequence will be computer generated in advance by a statistician of the coordinating office. A permuted blocks randomization approach will be used to allocate each participant to one of the two randomization groups. This method helps to ensure balanced number of patients assigned to each group. Each block size will be randomly selected between block sizes of 2, 4, 6 and 8, to avoid prediction of future patients' allocation. It will be stratified by centre, age (< or ≥ 65 years) and coma (RASS-4 or -5) at the beginning of invasive mechanical ventilation.

Allocation concealment

Only the independent statistician and the computer programmer who will implement the sequence assignment in the secure electronic case report form (eCRF) will have access to the randomization list Included subjects are allocated in a 1:1 ratio to restrictive PR use group (intervention group) or to systematic PR use group (control group). »

Page 20-21, statistical analysis.

1) Since patients are nested within provider and centers, please specify methods to adjust for clustering.

Response: Thank you for this remark. The randomisation is stratified on centres to allow the same ratio 1:1 between the two groups in each centre. The design is a parallel study design with patients as unit and not the centre as unit, therefore no clustering approach is required with this design. The centre effect will be assessed by testing interaction between trial arm and the centre in a linear regression modelling the number of delirium-free and coma-free days between D0 and D14. This analysis is mentioned in the section **Statistical analyses** and in the statistical analysis plan (Supplemental material 7, paragraph 3.3.16, Centre effect, age effect and presence of coma at beginning of IMV effect).

2) there are a large number of secondary outcomes. Please specify approach to adjust for multiple testing and avoid inflated family-wise type-1 error.

Response: Thank you for this suggestion. As showed by a rich and recent literature about the adjustment for multiple comparisons (Pike K, Reeves BC, Rogers CA. Approaches to multiplicity in publicly funded pragmatic randomised controlled trials: a survey of clinical trials units and a rapid review of published trials. BMC Med Res Methodol. 2022 Feb 6;22(1:39), different positions are proposed: On the one hande, in confirmatory studies, in which data are collected with prespecified key hypothesis, multiple test adjustments are not strictly required. On the other hand other investigators hold an opposite position that multiplicity corrections should be performed in confirmatory studies (Perneger TV. What's wrong with Bonferroni adjustments. BMJ. 1998 Apr 18;316(7139):1236-8. ; Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990 Jan;1(1):43-6).

As edited by Parker and Weir (Parker, R.A., Weir, C.J. Multiple secondary outcome analyses: precise interpretation is important. Trials 23, 27 2022) and Feise (Feise, R.J. Do multiple outcome measures require p-value adjustment? BMC Med Res Methodol 2, 8 (2002).) and Rothman (Rothman KJ. No adjustments are needed for multiple comparisons. Epidemiology. 1990 Jan;1(1):43-6), Multiple secondary outcomes are by definition subsidiary to primary outcomes, but this does not mean that they must necessarily be downgraded to the level of exploratory in the absence of multiplicity

adjustment. Indeed, if individual secondary outcome results are interpreted precisely, then the number of tests performed is irrelevant because the per-comparison-wise error rate is not increased.
What we are advocating is a careful and precise interpretation of secondary outcome results. Strong effects on secondary outcomes should always be taken seriously and must not be dismissed purely on the basis of multiplicity concerns. So, the following strategies should enable the reader to reach a reasonable conclusion, regardless of p-value adjustments (i) Evaluate the quality of the of the study and the amplitude (effect size) of the finding before interpreting statistical significance (ii) Regard all findings as tentative until they are corroborated. A single study is most often not conclusive, no matter how statistically significant its findings. Each test should be considered in the context of all the data before reaching conclusions, and perhaps the only place where "significance" should be declared is in systematic reviews.
Change in revised manuscript: we added the following paragraph to the limitations in discussion:
"We will not perform adjustments for multiple outcomes in the primary analyses due to all study outcomes being pre-specified hypotheses. In instances where significant effects on secondary outcomes are detected, we will examine post hoc results utilizing Holm and Hochberg procedures to derive adjusted p-values (Alosh M, Bretz F, Huque M. Advanced multiplicity adjustment methods in clinical trials. Stat Med. 2014 Feb 20;33(4):693-713)."

Reviewer: 3
Prof. Timothy Walsh, The University of Edinburgh
Comments to the Author:
This is a protocol for a trial which appears to be almost complete comparing two different approaches to physical restraint in the ICU. This is a topical and controversial topic, and use of restraint varies internationally between almost no use to almost routine use in ICUs.

1. Consent process (page 9. The protocol appears t state that the PI or a physician representing the investigator will make this decision. Can the authors clarify what legal ethical consent process governs this process? It says on page 13 that the relative will be 'informed' rather than provide consent or non-objection. There is further information on pages 20-21 but is not clear exactly how this process works. Perhaps a diagram explaining how the different consent stages and use of deferred versus relative consent works would be useful?
Response: we thank the reviewer for this comment. All participants provided informed consent, either directly or through a procedure of deferred consent. We clarified the manuscript accordingly.
Change in revised manuscript (page 10):
"All eligible patients (or their surrogates) will be informed about the study before randomization both verbally and with a written document, in accordance with French law. At the time of randomisation, written informed consent will be obtained from patients or surrogates through a process of deferred consent." "In brief, if the person is physically unable to give his or her written consent at time of randomization, he or she will be approached for written informed consent during follow-up after regaining capacity."

2. Consent for follow-up consent will be after regaining capacity (page 10). Again can the authors clarify what will be the case for patients who die or fail to regain capacity in terms of the legal basis for inclusion in the research?
Response: we thank the reviewer for this comment. We clarified the manuscript accordingly.
Change in revised manuscript (page 10):
"In brief, if the person is physically unable to give his or her written consent at time of randomization, he or she will be approached for written informed consent during follow-up after regaining capacity."

3. On page 10 the protocol states criteria for removal of PR in relation to agitation due to

delirium. Given there are other causes of agitation, for example pain, anxiety, drug withdrawal syndromes how will they manage agitation in this wider context?
Response : Management of analgesia, sedation, delirium in both groups is in the follow-up paragraph (ICU stay). We added a sentence in the Interventions paragraph to state this clearly.
Change in revised manuscript (page 10):
*"*In both groups, patients will have a standardized management of analgesia, sedation, delirium, MV weaning and early mobilization according to current guidelines (see paragraph follow-up)."

4. In Box 2 it would be informative to include what the 'eligible to physical restraint prescription' means as part of the actual inclusion criteria. This does not seem to be included in the text either and could be subjective and a source of bias or variation?
Response: As requested, we now provide information on this inclusion criterion. According to French law, the use of physical restraint is a medical decision deserving written prescription. We meant that all patients for whom physical restraint had already been prescribed were not eligible to randomization.
Change in revised manuscript (page 12):
*We added ("*not already restrained because of a previous medical prescription") in the footnote of box 2.*

5. Under outcomes there is quite extensive justification of each outcome. This might be better is the introduction or design section as it detracts from clarity about the actual outcomes being measured. There is also some repetition with the background/introduction.
Response: *We are sorry but we are not sure to fully understand this comment. In our opinion, study endpoints in Box 1 accurately reflect data presented in trial registry.*

6. On page 15 it may be useful to clarify how the sedation practice will be standardised, especially as agitation and delirium are likely to be closely linked to the practice of early light sedation either by titration by nurses and/or daily sedation holds/interruptions. There is description on page 16 of a number of aspects of care, but it could be clearer what is intended to be standardised across groups and sites.
Response: we thank Reviewer 3 for this important comment. We did not decide to modify sedation practices among centers. However, the use of "sedation stops" or "protocolized sedation (according to target RASS)" will be collected among participating centers, together with details on ventilator weaning protocols.
Change in revised manuscript (p16-17):
"Sedation practices will not be standardized among centers, and investigators will be asked to follow their local sedation protocol. For each participating centre, the type of sedation protocol ("sedation stop" or "protocolized sedation according to targeted RASS") and the use of daily spontaneous breathing trials for ventilator weaning will be collected."

7. Although I appreciate that this trial is already almost completed, the protocol does not describe any 'process evaluation', in other words how the authors will measure what actually happened in terms of following the protocol. There is a major expectation that staff will follow the two approaches being compared, with high chance of cross-over and/or deviation. It will be important to understand what the difference in use of restraint actually was in the trial, which may not be the same as the intended protocol. This is an important aspect of complex intervention trials.
Response: The data entry is conducted in real-time by designated research personnel at each center. It is then consolidated through comprehensive monitoring conducted monthly or bi-monthly, facilitating dynamic data management. For specific aspects regarding the use of PR, Comprehensive monitoring at the patient level will be conducted to ensure the acquisition of high-quality data

regarding adherence to the intervention or control arm (i.e. time spent with physical restraint), as well as to assess potential cross-contamination.

Change in revised manuscript (page 9):

"Comprehensive monitoring at the patient level will be conducted to ensure the acquisition of high-quality data regarding adherence to the intervention or control arm, as well as to assess potential cross-contamination."