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Restrictive use of Restraints and Delirium Duration in the Intensive Care Unit (R2D2-ICU): Protocol for a Multicentre Parallel-group Open Label Randomized Controlled Trial

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on behalf of the **R2D2-ICU investigators**

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ABSTRACT

Introduction Physical restraint (PR) is prescribed in patients receiving invasive mechanical ventilation in the intensive care unit (ICU) to avoid unplanned removal of medical devices. However, it is associated with an increased risk of delirium. We hypothesise that a restrictive use of PR, as compared to a systematic use, could reduce the duration of delirium in ICU patients receiving invasive mechanical ventilation.

Methods and analysis The Restrictive use of Restraints and Delirium Duration in ICU (R2D2-ICU) study is a national multicentric, parallel group, randomized (1:1) open label, controlled, superiority trial which will be conducted in 8 ICUs. 422 adult patients requiring invasive mechanical ventilation for an expected duration of at least 48 hours and eligible to prescription of PR will be randomly allocated within 6 hours from intubation to either the restrictive PR use group or the systematic PR use group, until day 14, ICU discharge or death, whichever comes first. In both groups, PR will consist of the use of wrist straps. The primary outcome will be the number of delirium-free and coma-free days, defined as the number of days spent alive in the ICU without coma or delirium within the first 14 days after randomisation. Delirium will be assessed using the CAM-ICU twice daily. Secondary outcome will be incidence and duration of delirium, exposure to analgesic, sedative or antipsychotic drugs, pressure ulcers, complications related to delirium over 14 days and a core outcome set of secondary measures 90 days after inclusion.

Ethics and dissemination The R2D2 study has been approved by the Comité de Protection des Personnes (CPP) ILE DE FRANCE III – PARIS (CPP19.09.06.37521) on 06/10/2019). Participant recruitment started on January 25th, 2021. Results will be published in international peer-reviewed medical journals and presented at conferences.

Trial registration number NCT05248035, first posted on February 18th, 2020.

STRENGTHS AND LIMITATIONS

- A large multicentre randomized controlled trial evaluating the impact of physical restraint on the duration of delirium among mechanically ventilated patients in the intensive care unit (ICU).
- A clinically relevant primary outcome measure, i.e., the number of delirium-free and coma-free days, defined as the number of days spent alive in the ICU without coma or delirium within the first 14 days after randomisation.
- A follow-up at 90 days with a core outcome set of secondary measures.
- The study will provide important information about the safety of physical restraint in the ICU setting.
- Due to the open-label design of our study, we will standardize the delirium assessment and management in both groups according to international guidelines.

INTRODUCTION

Background and rationale

The application of physical restraint (PR) within intensive care units (ICUs) has been a customary practice aimed at ensuring patient safety and averting the inadvertent removal of medical devices. However, studies have revealed substantial variability in the prevalence of PR use, with rates spanning from 0% to 100% in European ICUs [1]. Patients subjected to PR were more likely to be ventilated, sedated, and managed in larger units with lower nurse-to-patient ratios.

Interestingly, only a minority of ICUs possessed a written protocol for PR use, underscoring the absence of standardized guidelines in this field [2]. In a randomised trial of protocolised sedation, PR was utilised in 76% of patients for a median duration of 4 days [3]. Additionally, a survey in French centres disclosed that PR was employed in over 50% of mechanically ventilated patients in 82% of ICUs, with a lack of written local procedures in the majority of cases [4].

In contrast to the extensive use of PR in ICUs, the American guidelines on pain, agitation, and delirium management do not furnish specific recommendations for PR use [5]. Agitation in ICU patients, observed in 52% of cases in a French study, was associated with adverse outcomes, including prolonged ICU stay, nosocomial infections, and unplanned extubation [6]. In a prospective study conducted in 51 ICUs in Canada, treatment characteristics seem to predict PR use (higher daily doses of benzodiazepines and opioids, antipsychotic drugs, and agitation), as opposed to patient or ICU characteristics [7].

Despite the commonplace application of PR, its benefits in critically ill patients remain unestablished, and it may even be deleterious, by causing injury, agitation, and psychological distress for patients and families. PR has been linked to adverse psychological effects, including stressful memories for survivors of critical illness [8]. Moreover, its complex association with brain dysfunction, manifested as agitation and/or delirium, raises concerns. While PR is intended to mitigate the potential risks associated with agitation, it appears to favor the development of delirium [9]. In a recent study, the risk of use of PR

was increased in patients with delirium or coma, in patients who could not communicate verbally, and in patients receiving psychoactive or sedative drugs [2].

Delirium, defined as a disturbance in attention and awareness developing over a short period of time, is common occurrence in critically ill patients receiving invasive mechanical ventilation. It is associated with poor outcomes, including higher morbidity and mortality [10], and long term cognitive impairment in survivors [11].

Recent research emphasizes the need to better understand delirium mechanistically to facilitate prevention and treatment [12]. In this context, PR may represent a modifiable risk factor for delirium in ICU patients [13,14]. The number of days without delirium in the ICU is significantly associated with both short-term mortality and long-term cognitive impairment, suggesting the potential importance of addressing PR practices in the ICU to improve patient outcomes [15].

Hypothesis

We hypothesize that a restrictive use of PR, as compared to a systematic use, could reduce the duration of coma and delirium among patients receiving invasive mechanical ventilation in the ICU.

Objectives

Study objectives and associated endpoints are presented in **Box 1**. The primary objective is to assess whether a restrictive use of PR, as compared to a systematic use, decreases delirium duration during the first 14 days after randomization. The 15 secondary objectives are presented in the **Box 1.**

Box 1 Study objectives and associated endpoints

Primary objective	**Primary endpoint**
To assess whether a restrictive use of PR, in comparison to a systematic use, decreases delirium duration during the first 14 days after randomization (D0).	**Delirium or coma-free days, defined by the number of days alive without delirium (measured by CAM-ICU) or coma (measured by RASS) during the first 14 days (D14) after randomization (D0)**
Secondary objectives	**Secondary endpoints**
To evaluate the effect of restrictive use of PR between D0 and D14 on: ➢ Incidence of delirium ➢ Agitation duration ➢ Exposure to opioids ➢ Exposure to propofol ➢ Exposure to benzodiazepines ➢ Exposure to antipsychotic agents ➢ Exposure to dexmedetomidine ➢ Exposure to MV ➢ Patient mobility according to the visual mobilisation score ➢ Incidence of self-extubation and device removal ➢ Skin lesions occurrence	➢ percentage of patients with at least one day of delirium (positive CAM-ICU) between D0-D14 ➢ Number of days alive with agitation (RASS score ≥ +2) between D0-D14 ➢ Total cumulative dose of opioids infusion between D0-D14 ➢ Total cumulative dose of propofol infusion between D0-D14 ➢ Total cumulative dose of benzodiazepines infusion between D0-D14 ➢ Total cumulative dose of antipsychotics infusion between D0-D14 ➢ Total cumulative dose of dexmedetomidine infusion between D0-D14 ➢ Invasive mechanical ventilation-free hours between D0-D14 ➢ Median of Mobilisation capacity and rate of patients > 2 on a visual scale (SOMS) ranging from 0 (no mobilisation) to 4 (ambulation) between D0-D14 ➢ Rate of patients with at least one self-extubation or any device removal between D0-D14 ➢ Rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel (at least one ulcer of grade III or IV per patient) between D0-D14
To evaluate the effect of restrictive use of PR until ICU Discharge on: ➢ Delirium duration until ICU discharge: Patients will be considered “ready for discharge” as soon as all clinical conditions for ICU discharge will be fulfilled ➢ ICU and hospital lengths of stay	➢ Number of days on delirium until ICU discharge ➢ Number of days of ICU stay and of hospital stay [up to D90] ➢ Death rate during ICU stay and hospital stay [up to D90]

➢ In-ICU and in-hospital mortality	
To evaluate the effect of restrictive use of PR at D90 (after inclusion) on the global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD)	➢ Rate of patients with at D90 an altered cognitive capability defined as a MMSE (Mini Mental State Examination) ≤ 24 points ➢ Rate of patients with a frontal syndrome defined as a FAB (Frontal Assessment Battery at Bedside) < 15 points ➢ Rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder (PTSD) defined as a R-IES (Revised-Impact of events scale) ≥ 33 points ➢ Rate of patients with a functional disability defined as a GOS-E (Glasgow Outcome Scale - Extended) ≤ 6 points ➢ Functional independence status (yes or no) evaluated by the FIM (functional independence measurement) scale

CAM-ICU: Confusion Assessment Method for Intensive Care Unit; D: Day; IMV: Invasive Mechanical Ventilation;

METHODS AND ANALYSIS

Design overview

The R2D2 study is an investigator-initiated, national multicentric, superiority, open label parallel-group, comparative controlled randomized trial, in which patients being on invasive MV in the ICU for a duration inferior to 6 hours are allocated in a 1:1 ratio to restrictive PR use group (intervention group) or to systematic PR use group (control group). The trial design is summarised in **table 1** and in **figure 1**. We report the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials statement (**supplementary material 1**) [16]. The selection of a parallel group design, randomised with two interventions, one of which includes systematic PR, allows for the elimination of service-specific practices, and focuses on patient-centred considerations. The practice guidelines outlined in the protocol for each group will facilitate standardised management, thereby minimising the risk of cross-contamination.

Patient inclusion and randomization will be conducted either by the principal investigator or by a physician representing the investigator. Patient eligibility will be assessed in accordance with the predefined inclusion and exclusion criteria. Each centre will maintain a screening log for all eligible

patients. The use of physical restraint will involve the use of wrist straps, precluding a blind investigation of group assignments.

During the follow-up period, patients who regain capacity will be approached for written informed consent. The observation period for patients will extend from the time of inclusion until their discharge from the ICU or until their demise, with a specific follow-up consultation scheduled at Day 90 for all surviving patients.

Interventions

For all patients, PR will consist of the use of wrists straps. The restrictive or systematic strategies will be applied until one of the following events occur, whichever comes first: a) day 14 in ICU; b) ready for "ICU discharge" (Patients will be considered "ready for discharge" as soon as all clinical conditions for ICU discharge will be fulfilled (i.e., no more need for vital-organ support, and no more need for central or arterial catheter); c) death before day 14.

Intervention group

In the restrictive PR use group, patients will be subjected to PR only in case of severe agitation, defined by a RASS score ≥ +3 on any given day between day 0 and day 14.

Control group

In the systematic PR use group, patients will be systematically subjected to PR, which will be re-evaluated every day every day between day 0 and day 14. The removal of PR will be allowed when patients meet any of the following criteria: 1) Awake without delirium, defined by a RASS > -4 and a negative CAM-ICU; 2) Extubated without delirium, defined by the absence of invasive MV and a negative CAM-ICU. The PR will be resumed in case of severe agitation, defined by a RASS ≥ +3 on any given day between day 0 and day 14, irrespective of the need for invasive MV.

Box 2 Eligibility criteria

Eligibility criteria

- ✓ Patient requiring Invasive mechanical ventilation for an expected duration of at least 48 hours

Inclusion criteria

- ✓ Adult (over 18 years old)
- ✓ Invasive mechanical ventilation in the ICU for a duration inferior to 6 hours
- ✓ Eligible to physical restraint prescription

Exclusion criteria

- ✓ Documented delirium prior to ICU admission according to the CAM-ICU
- ✓ History of dementia (MMS-E < 24)
- ✓ Alcohol withdrawal syndrome expected
- ✓ Admission for any neurological disease including post-cardiopulmonary resuscitation (including cardiac arrest, stroke, traumatic brain injury, meningoencephalitis, and status epilepticus)
- ✓ Serious auditory or visual disorders
- ✓ Unable to understand French
- ✓ Pregnant or lactating women
- ✓ SAPS II > 65 points at screening
- ✓ Do-not-resuscitate orders
- ✓ No affiliation of the French social security regime (beneficiary or assignee)
- ✓ Patient or person of confidence (if present at the time of inclusion) opposing the patient's participation in research
- ✓ Patient already involved in another interventional clinical research whose main objective is related to delirium

ICU: Intensive Care Unit; CAM ICU Confusion Method Assessment in the ICU; IMV: Invasive Mechanical Ventilation; MMS-E: Mini Mental State Examination; SAPS2: Simplified Acute Physiology Score 2.

Table 1. Summary of the chronology of the study with data collected

Timepoints	Screening D0	Randomisation D0	D1 to D14	Discharge	D90
Description of timepoints	Within 6 hours after beginning of IMV		0 to 14	Day of ICU and hospital discharge	90 days after randomization
Eligibility screen	X	X			
Informed consent*		X			
SAPS2	X	X			
SOFA	X	X			
Assessment					
Admission variables		x			
Demographics		x			
Comorbid conditions		x			
Drug/alcohol consumption		X			
Benzodiazepine treatment		X			
Cognitive impairment		X			
Braden scale		X			
BPS		X	X		
SARS-CoV-2 status	X				
Main reason of IMV		X			
Outcome variables					
RASS (twice a day)		X	X		
CAM-ICU (twice a day)		X	X		
Sedatives (propofol, benzodiazepines, and dexmedetomidine)			X		
Opioids			X		
Antipsychotics			X		
Agitation					
Self-extubation			X		
Accidental removal of medical devices			X		
Mobilization by visual scale			X		
Skin lesions			X		
Length of stay (ICU and Hospital)			X	X	X
Vital status			X	X	X
Follow-up consultation (mRS, MRC, MMS-E, FAB, IES-R, GOS-E, FIM, IPREA scales)					X

IMV Invasive Mechanical ventilation, RASS Richmond Agitation Sedation Scale, CAM-ICU Confusion Assessment Method for the ICU, MMSE Mini Mental State Evaluation, FAB Frontal Assessment Battery, IES-R Impact of Events Scale-revised, IPREA Inconforts des Patients de REAnimation, GOS-E Glasgow Outcome Scale-Extended, FIM Functional Independence Measure, MRC Medical Research Council Scale, ICU Intensive Care Unit, SAPS2 Simplified Acute Physiology Score 2, SOFA, Sequential Organ Failure Assessment, BPS behavioural pain scale, MV mechanical ventilation.

* not mandatory, emergency inclusion is authorized by the French regulatories. In case of emergency inclusion, close relative and/or patient inform consent will be collected as soon as possible

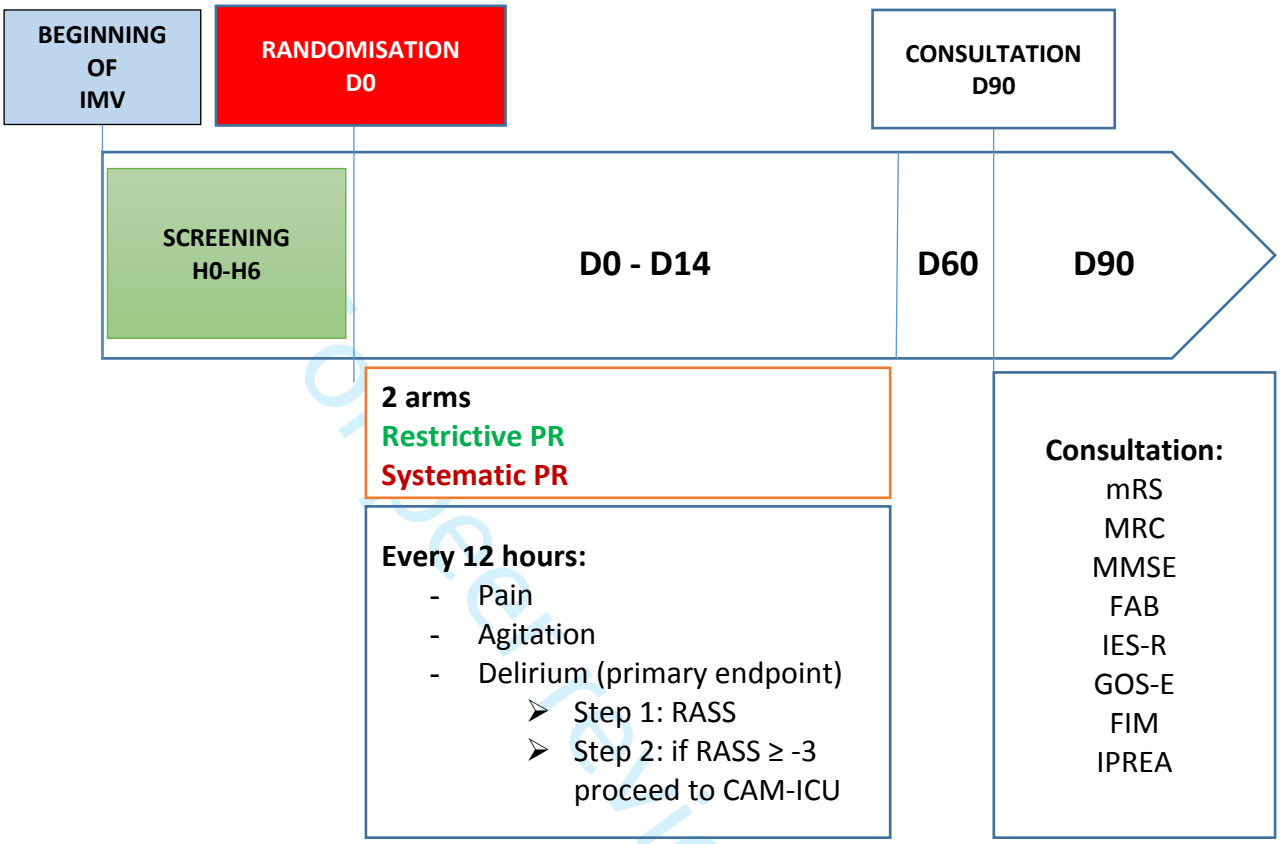

Figure 1. Flow diagram.

IMV Invasive Mechanical ventilation, RASS Richmond Agitation Sedation Scale, CAM-ICU Confusion Assessment Method for the ICU, MMSE Mini Mental State Evaluation, FAB Frontal Assessment Battery, IES-R Impact of Events Scale-revised, IPREA Inconforts des Patients de REAnimation, GOS-E Glasgow Outcome Scale-Extended, FIM Functional Independence Measure, MRC Medical Research Council Scale.

Study setting and population

Patients will be prospectively recruited among patients admitted in 10 French ICUs, which an onset of invasive MV in ICU less than 6 hours and with invasive MV expected for at least ≥ 48 hours. The close relative will be informed for inclusion of the patients in the R2D2 trial by the by the intensivist physician investigators during the screening phase (see figure 1). Patients will be considered eligible for enrolment if they fulfil the inclusion criteria and none of the exclusion criteria, as defined in **BOX 2**.

Outcomes

Primary endpoint

The primary outcome is the number of delirium-free and coma-free days, defined as the number of days in the first 14 days after randomization during which the patient was alive without delirium and not in coma from any cause. Brain dysfunction in the ICU, i.e. delirium or coma, is serious event in critically ill patients that is associated with prolonged hospital stays, costs, increased mortality and cognitive impairment in survivors. In this regard, the number of days alive without delirium or coma in the ICU has emerged as a clinically relevant endpoint in critical care trials [17,18]. Moreover, duration of delirium in the ICU is associated with important patient-centred outcomes. It has been recently suggested that a longer duration of delirium in the ICU was associated with worse global cognition and executive function at 12 months following ICU discharge [19].

This end-point will be assessed twice a day and if needed according to patients' clinical status by the French validated translation of the Richmond Agitation Sedation Score (RASS) [20] and CAM-ICU [21] by well-trained nurses as recommended by the 2013 clinical practice guidelines for Pain, Agitation, and Delirium (PAD) in ICU patients [5]. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score > or = -3 will be assessed for delirium with the use of the CAM-ICU scale **(see supplemental material 2).**

The Society of Critical Care Medicine (SCCM) Pain Agitation and Delirium [5] guidelines recommends 1/ the use of sedation scales to assess arousal level 2/ then, if patients are assessable, the use of validated tools to assess for delirium, such as the Confusion Assessment Method-ICU (CAM-ICU) [21]. All four domains of the CAM-ICU, anchored on the presence of inattention, are evaluated in a focused patient assessment usually taking less than 2 min to complete. The CAM ICU scale is recognized as one of the leading assessment tools for delirium in the ICU. It has undergone extensive development, validation, and is routinely utilized with a once-daily assessment [22,23].

Secondary endpoints

the full list of secondary endpoints is provided in **Box 2**.

Randomization and sequence generation

The randomisation will be performed using CleanWEB, a 24/7 online centralise procedure service running. The randomisation sequence will be computer generated in advance by a statistician of the coordinating office. 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

The number of experimental units per block will be kept confidential to avoid prediction of future patient's allocation. 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. Allocation concealment will be ensured, as CleanWeb services will not release the randomization code until the patient has been recruited into the trial. Patient allocation will only be disclosed after the enrolment and the dedicated statistician will be blinded to the arm's allocation until the end of analysis.

Follow-up

ICU stay

In both groups, patients will have a standardized management of analgesia, sedation, delirium, MV weaning and early mobilization according to current guidelines [5]. This will ensure that the tested strategy is efficient by itself when applied along with other recommended clinical practices in ventilated patients, especially those known to have an impact on delirium occurrence. Nurses in charge will have at their disposal a daily sheet including standard surveillance and clinical pathways to follow according to surveillance (see next page). Clinical pathways aim to plan, rationalize and standardize multiprofessional management of patients with similar health problems based on recommendations to limit the variability of practices. Clinical pathways also ensure the traceability of these practices. Our clinical pathways were established according to HAS guidelines taking into account current guidelines to manage ICU patients on MV [5]. The daily sheets from D0 to D14 will be grouped in a booklet in A3

format to ensure better readability. An explicit training to use the booklet and the clinical pathways is planned before the start of the study (**see supplemental materials from 3 to 6**) and include:

1) Routine pain, agitation and delirium assessment will be performed every 12 hours (and more frequently as needed) using valid and reliable assessment tools, i.e BPS (behavioural pain scale [24], RASS [20] and CAM-ICU [21] in accordance with PAD guidelines [5].

2) Management of pain, agitation and delirium can be summarized as follows:

- Analgesia will be adapted to maintain BPS ≤ 4. Patients will be considered to be in significant pain if they have a BPS score of 6 or greater.
- Sedation will be adapted continuously to maintain a RASS score compatible with patient's management, i.e. from -1 to +1 (i.e., drowsy/alert to calm/restless) in general cases and from -5/-4 to -3 (i.e. deep sedation to moderate sedation) in case of severe acute respiratory distress syndrome (ARDS) or refractory intracranial hypertension.
- In case of RASS score ≥ -3 assess delirium every 12 hours using CAM-ICU and more often as needed.
- In case of significant pain (BPS ≥ 6), agitation (RASS ≥ +2) or delirium (CAM-ICU positive), the nurses will refer to specific clinical pathways including a physician alert process.

3) Clinical pathways to manage agitation will differ between groups since severe agitation with a RASS score ≥ +3 will require a temporary physical restraint (< 24 hours) in the restrictive use of PR group.

The PAD management strategies will be associated with other ICU interventions that are known to impact delirium occurrence or duration, i.e spontaneous awakening trial (SAT), spontaneous breathing trial (SBT) and early mobilization (EM) protocols.

The observation period of patients will be from inclusion until ICU discharge or death with a specific consultation at D90 for all alive patients.

Follow-up consultation at D90

A dedicated consultation will be performed at D90 by a psychologist (or an investigator or a study coordinator formed to the following tests). That consultation will be carried out first in the hospital, if

this is not possible it can be carried out by teleconsultation. If the follow up is carried out by teleconsultation, an information note, specifying that no recording of the consultation will be made, will be sent to the patient when programming the follow-up. The non-objection of the patient will be sought and noted in the medical file.

During this consultation:

- The psychologist will assess cognitive capabilities using the MMSE (Mini Mental State Examination) and the FAB (Frontal Assessment Battery)
- The psychologist will search for a post-traumatic stress disorder (PTSD) using the R-IES-R (Revised-Impact of Events Scale).

Furthermore the following data will be collected: care pathways since the hospitalization in intensive care (start and end of hospitalization session(s), consultation(s)), the functional state GOS-E, Rankin; MRC; thirst, anxiety and sleep quality (IPREA-SFAR scale [25]) and MIF, living environment, home supports, date of return to work if appropriate.

- If the visit did not take place, the following data will be collected by telephone from the patient or his / her family, if applicable: care pathways since the hospitalization in intensive care (start and end of hospitalization session(s), consultation(s)), the functional state GOS-E and MIF, living environment, home supports, date of return to work if appropriate.

STATISTICAL CONSIDERATIONS

Sample size calculation

In the literature, the number of delirium-free and coma-free days between D0 and D14 is estimated at 10.5 ± 3 days in the systematic PR group [6,26]. We therefore expect a 1-day reduction in delirium duration in the restrictive PR group with a number of delirium-free and coma-free days estimated at 11.5 days. We assumed a sample of 191 inclusions per arm to achieve 90% power to detect a difference of 1 day in the mean number of delirium-free and coma-free days over 14 days between the two groups at a 0.05 significance level. To allow the require power for the per-protocol analysis the sample size required is 422 (allowing for an estimated 9% loss to follow-up). Relying on the active participation of

the 10 participating centres, we estimate that the inclusion time will be 38 months (Assuming the number of inclusions at 1.1 patients per month per centre). To ensure the 422 planned inclusions and the 3-month follow-up of all included patients, a research duration of 41 months is expected. Participant recruitment started on January 25th, 2021.

Statistical analyses

The number of delirium-free and coma-free days between D0 and D14 will be compared between the two experimental groups, systematic use group vs. restrictive use group by a Student's test or a Wilcoxon Rank-Sum test if no normality of criteria.

If the patient dies within 14 days, the number of non-surviving days will be considered days of coma. If the patient is discharged before D14, after extubation, the number of days remaining will be considered delirium-free and coma-free days. If the patient is discharged before D14, always in MV, the number of days remaining will be considered delirium days.

The main analysis will be in intent to treat (ITT), that is, patients will be analysed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analysed in the arm of management received. For the analysis of patients who leave the service before D14, we will perform a sensitivity analysis, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14, by a linear regression with adjustment on these 3 continuous factors. 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.

We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of IMV. In case if significant interaction, a sub-group analysis will be performed.

Secondary analyses will be performed in ITT and then in Per-protocol. The continuous secondary criteria of duration and cumulative doses of sedative agents', analgesics and or antipsychotics between D0 and D14 will be compared between the two experimental groups, systematic use group vs. restrictive use group, by a Student test or a Wilcoxon Rank-Sum test.

The categorical secondary criteria will be compared by a Chi-square test or an exact Fisher test if appropriate.

The significant level of all statistical analyses will be a two-sided 5% and the confidence interval at 95%. All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 4.0 or later. All analyses will be conducted by a statistician according to a prespecified statistical analysis plan. A full statistical analysis plan has been written and is available in **supplemental material 7**. All analyses results will be reported according to the Consolidated Standards of Reporting Trials (STROBE) 2010 guidelines [27].

Data collection and management

Data collection will be done in electronic format using CleanWeb software. The software will fulfil the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

We will collect data on primary and secondary endpoints, as well as potential risk factors of delirium (ICU medication, comorbidities and complications) detailed in **table 1**.

The data of this study will be available upon reasonable request from the corresponding author. The data will not be publicly available due to privacy or ethical restrictions.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in any of the phases of this study. Results of the trial will be made available to all participants via ClinicalTrials.gov as well as by email notification.

TRIAL STATUS

Recruiting. The first inclusion occurred on the 21th of January 2021 and the recruiting period will last 39 months. On December first, 400 patients have been included.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this non-interventional human research study. AP-HP has obtained the favourable opinion of the independent ethics committee "Comité de Protection des Personnes (CPP) ILE DE FRANCE III – PARIS (CPP19.09.06.37521) for the study protocol (version R2D2–05.0; March 3, 2023). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol must be sent to the sponsor for approval. Once approval has been received from the sponsor, it must also obtain approval from the CPP before the amendment can be implemented. The information sheet and the consent form can be revised, if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research mentioned in 3° of this article (like R2D2 protocol) can be carried out on a person without his/her free and informed non opposition, obtained in oral after the person has been given the information specified in Article L.1122-1 of said Code.

The trustworthy persons/relatives of eligible patients will be informed of the modalities of implementation of the study through an information note and a consent form (see supplemental material 1) and oral explanations given by the investigating physician or any qualified person. This information and consent forms will also be given to the patient concerned as soon as his neurological condition allows it.

Indeed, at the time of inclusion, the person participating in the research is often not in a state to give their consent; the inclusion in the R2D2 protocol is therefore done without prior agreement of the patient. Inclusion in the R2D2 protocol is done as soon as the patient is consecutively hospitalized in ICU and requires IMV: it is therefore not always possible to obtain the consent of the person before his inclusion in the trial.

The protocol therefore provides that the consent of this person is not systematically sought at inclusion and that only the non-opposition of family members or the trusted person is sought, and the informant (investigator or collaborator) will have sufficient time (the first 3 days of the patient's resuscitation) to proceed with clear and informed information, imperatively before the patient's inclusion in the research.

The information will be given to the patient and his consent will be sought at the time when his neurological state allows it.

The information and the collection of the consent of the patient or trusted person/relative is collected by the principal investigator, or by a physician who represents him/her, or by a qualified person in the participating centre.

Thus, 2 types of information document are provided for:

- one for the trusted person/close relative if he/she is present at the time of inclusion when the patient is unable to be informed.

- one for the patient as soon as he/she is able to consent to the continuation of the research.

A copy of the information document is given to the person participating in the research. The information given to the subject will be recorded in his or her medical file. Subjects may exit the study at any time and for any reason.

DATA COLLECTION AND QUALITY CONTROL

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information relating to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. Under no circumstances should the names, addresses and other protector identifiers of the subjects involved be shown.

A data monitoring committee (DMC) has not been convened, on the grounds that the study is low risk. This has been approved by the Sponsor, Steering Committee, and the independent Ethical Board. The research data will be collected and monitored using an eCRF through CleanWEB Electronic Observation Book and will be centralised on a server hosted by the AP-HP Operations Department. This research is governed by the CNIL 'Reference Method for processing personal data for clinical studies' (MR-001, amended). AP-HP, the sponsor, has signed a declaration of compliance with this 'Reference Method'.

An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording, and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by independent individuals appointed by the sponsor. The aims of the audits are to ensure the quality of the study, the

validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

SAFETY CONSIDERATIONS

The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests. The physical restraint will be prescribed in case of agitation (see guideline in supplemental materials).

TRIALS OVERSIGHT COMMITTEES

Two oversight committees have been established to oversee the conduct of this trial, the Steering Committee and Scientific Committee, the composition of each is listed at the end of this paper.

PUBLICATION PLAN

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and the publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the R2D2 investigators' in the final manuscript. Rules on publication will follow international recommendations.[28]

Author contributions RS and LB contributed to the conception and design of the research protocol, assisted by CC and VG. RS, CC, and LB wrote the first draft of the protocol and this manuscript. RC designed the statistical analysis plan. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interest statement Romain Sonneville received grants from the French Ministry of Health and from LFB. Other authors declare no competing interests.

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PARIS, grant number PHRC-N 2017. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

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Restrictive use of Restraints and Delirium Duration in ICU (R2D2-ICU): protocol for a multicenter parallel-group open label randomized controlled trial

SUPPLEMENTAL MATERIAL 1: SPIRIT CHECKLIST

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4 P20
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P20
Funding	4	Sources and types of financial, material, and other support	P24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 P23
	5b	Name and contact information for the trial sponsor	P1 P24
	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	P23
	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)	P23
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	P6

	6b	Explanation for choice of comparators	P6 P10
Objectives	7	Specific objectives or hypotheses	P7 BOX1
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)	P9 P15
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	P13
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)	P10 BOX2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10 TABLE1
	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)	P10 SM3-SM6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P21
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P23 TABLE1 SM3-SM6
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	P14 BOX1
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)	TABLE1 FIGURE1
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	P17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P13

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	P15
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	P15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P15 P21
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P15

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	P21
	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	P21
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	P21
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	P17 SM7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P17 SM7
	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)	P17 SM7

Methods: Monitoring

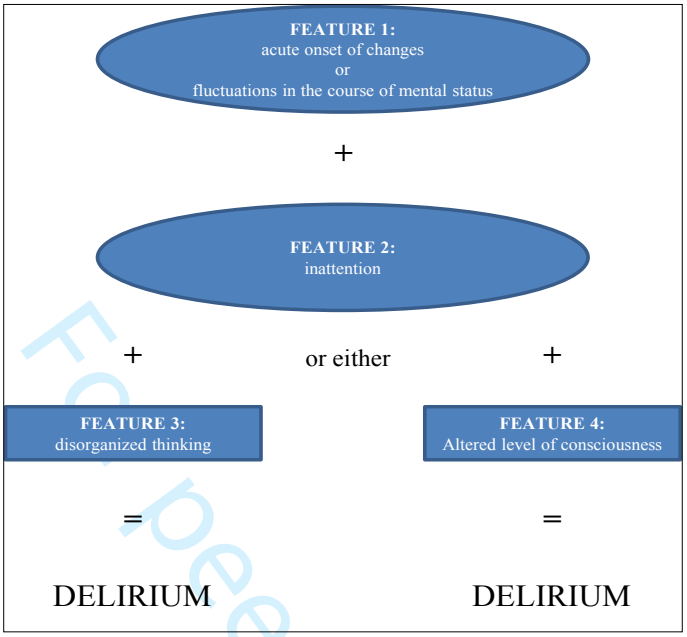
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NOT APPLICABLE
	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	NOT APPLICABLE
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	P21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NOT APPLICABLE
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P20
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)	P20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P9 TABLE1 P19 P20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NOT APPLICABLE
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	P20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P24
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	P20
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	NOT APPLICABLE

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	P20
	31b	Authorship eligibility guidelines and any intended use of professional writers	P20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NOT PROVIDE
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	NOT APPLICABLE

SUPPLEMENTAL MATERIAL 2: DELIRIUM ASSESSEMENT

CAM = Confusion Assessment Method

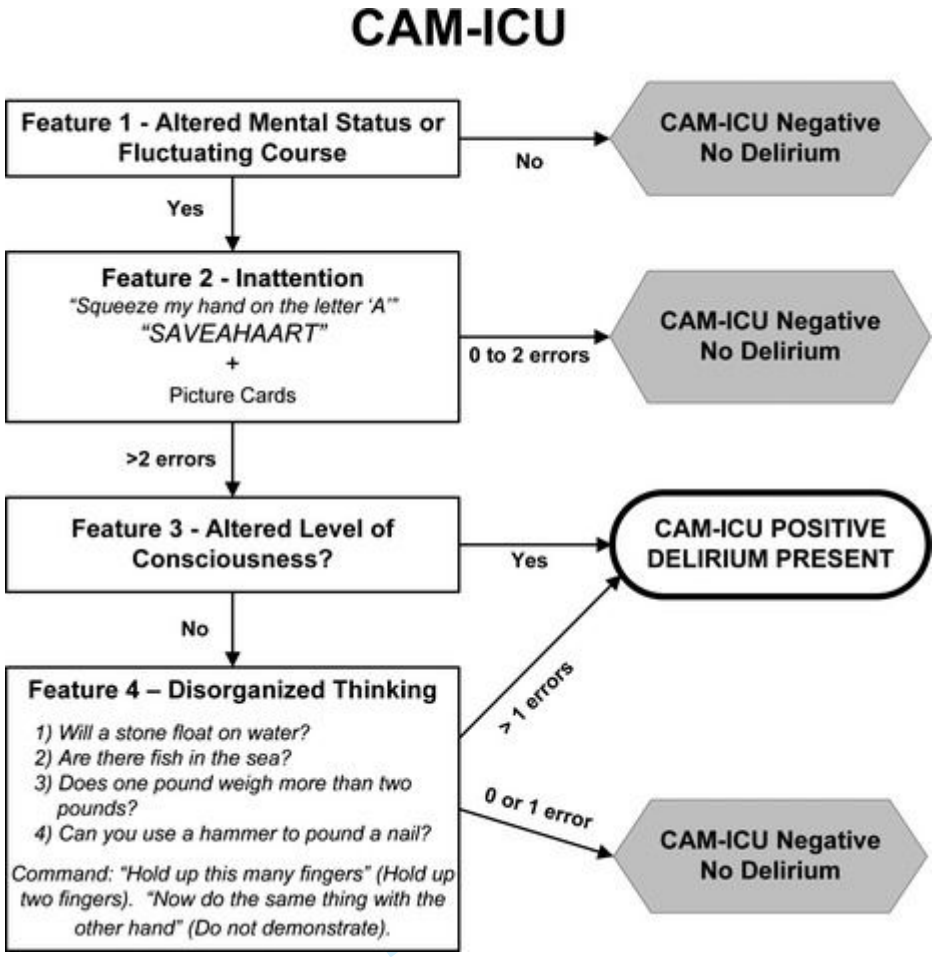
The Confusion Assessment Method (CAM) was created in 1990 by Dr. Sharon Inouye, and it was intended to be a bedside assessment tool usable by non-psychiatrists to assess for delirium [38]. Delirium is defined in terms of four diagnostic features, and is deemed positive when Feature 1 and Feature 2 and either Feature 3 or 4 are present (see CAM and CAM-ICU schematics).



CAM Confusion Assessement Method		
	The diagnosis of delirium by CAM requires the presence of **BOTH** features ***A*** and ***B***	
	A = acute onset and fluctuating course	Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: ➢ come and go? ➢ fluctuate during the day? ➢ increase/decrease in severity?
	B = Inattention	Does the patient: ➢ have difficulty focusing attention? ➢ become easily distracted? ➢ have difficulty keeping track of what is said?
	AND the presence of **EITHER** feature **C** or **D**	
	C = Disorganized thinking	Is the patient's thinking ➢ disorganized ➢ incoherent For example does the patient have ➢ rambling speech/irrelevant conversation? ➢ unpredictable switching of subjects? ➢ unclear or illogical flow of ideas?
	D = Altered level of consciousness	Overall, what is the patient's level of consciousness: ➢ alert (normal) ➢ vigilant (hyper-alert) ➢ lethargic (drowsy but easily roused) ➢ stuporous (difficult to rouse) ➢ comatose (unrousable)

The Confusion Assesement Method for the Intensive Care Unit (CAM-ICU)

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course A. Is there evidence of an acute change in mental status from baseline? **B.** Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidence by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Coam Glasgow Scale?	☐	☐
II. Inattention Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answerson either the visual or auditory components of the Attention Screening Examination (ASE)	☐	☐
III. Disorganized thinking Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stonefloat on water 2. Are there fish in the sea 3. Does 1 pound weigh more that 2 pounds 4. Can you use a hammer to pound a nail Commands 1. Are you having unclear thinking? 2. Hold up this many fingers(examiner holds 2 fingers in front of the patient) 3. Now do the same thing with the other hand (withoutholding the 2 fingers in front of the patient) (If the patient is already extubated from the ventilator, determine wether the patient's thinking is disorganized or incoherent, sucha s rambling or irrelevant conversation, unclear or illogical flow or ideas, or unpredictable switching from subject to subject)	☐	☐
IV. Altered level of consciousness Is the patients's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environement and interacts appropriately Vigilant: hyperalert Lethargic drowsy but easily aroused, unaware of some elements in the environement or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unware of some or all elements, in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapes back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding	☐	☐
Overall CAM-ICU Assessment (Features I and II and either feature III or IV): YES ☐ NO ☐		



The CAM-ICU is an adaptation of the CAM tool for use in ICU patients (e.g., critically ill patients on or off the ventilator) using nonverbal, objective tests derived through a comprehensive literature review and consulation with numerous delirium experts. (1). The CAM-ICU underwent extensive validation in the ICU setting and is, therefore, one of the delirium scores recommended by international guidelines (2). The Richmond Agitation Sedation Scale (RASS) is a component of the CAM-ICU (Feature 4: Altered Level of Consciousness).

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SUPPLEMENTAL MATERIAL 3: DAILY CRITICAL CARE MANAGEMENT OF SYSTEMATIC PHYSICAL RESTRAINT

GROUP
SYSTEMATIC PHYSICAL RESTRAINT

DATE
From D0 to D14 __ __/__ __/____

SCHEDULE (X = mandatory; x = if needed)	AM					PM												AM						
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
PAIN/SEDATION-AGITATION/DELIRIUM ASSESSEMENTS																								
I : Assess pain using BPS: TARGET ≤ 4 Refer to the specific clinical pathway on the back of the sheet if BPS > 4.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
II : Assess agitation/sedation using RASS : TARGET -1/0/+1 (-4/-5 in case of ARDS or ICH) Refer to the specific clinical pathway on the back of the sheet if RASS ≥ +3. **Mention physical restraint session |----|**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
III : Assess delirium only if RASS ≥ - 3 using CAM-ICU **Refer to the specific clinical pathway on the back of the sheet** criteria I +II and criteria III and /or IV present - Criteria I present (Yes/No) - Criteria II present (Yes/No) - Criteria III present (Yes/No) - Criteria IVpresent (Yes/No)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY SCREEN																								
I : SAT safety screen Follow and complete the clinical pathway on the back sheet. If appropriate do SAT and go to SBT. Mention both sedatives STOPS (SAT) and RESTARTS (R) times.	ONCE A DAY BETWEEN 8AM AND NOON																							
II : SBT safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do SBT. Mention both SBT, EXTUBATION (E), and REINTUBATION (R).	ONCE A DAY BETWEEN 8AM AND NOON																							
III : EM safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do EM according to patients'status Mention both (MAP, MAA, PV, BL, MFP, MFA, walk)	ONCE A DAY BETWEEN 8AM AND NOON																							

BPS = Behavioral pain scale; RASS = Richmond Agitation-Sedation Scale; SAT= spontaneous awakening trial; SBT = spontaneous breathing trial; EM = early mobilization

SUPPLEMENTAL MATERIAL 4: CLINICAL PATHWAYS ACCORDING TO BPS, RASS AND CAM-ICU ASSESSMENTS FOR THE SYSTEMATIC PHYSICAL RESTRAINT GROUP

Clinical pathways according to BPS, RASS, and CAM-ICU assessments

SIGNIFICANT PAIN: BPS ≥ 6

REFER TO THE PHYSICIAN IN CHARGE

1) Diagnose the source of pain

Check for a serious painful event (myocardial infarction, thromboembolic event, ileus, peritonitis)

2) Choose the appropriate analgesic

a. Use the WHO analgesic scale to treat a nociceptive pain.
   First WHO level: acetaminophen and/or nefopam
   Second WHO level: dextropropoxyfen or tramadol or nalbuphin.
   Third WHO level: morphine or fentanyl or patient-controlled analgesia.

b. Use a spasmolytic intestinal drug to treat an intestinal spasm.

c. Use centrally acting muscle relaxants to treat a muscle contracture.

d. d. Use anti-inflammatory nonsteroid drugs (AINS) to treat an inflammatory pain if first and second WHO level analgesics are inefficient.

SIGNIFICANT AGITATION: RASS ≥ +2

REFER TO THE PHYSICIAN IN CHARGE

1) Physical restraint if RASS ≥ +3

2) Diagnose the source of agitation*

3) Choose the appropriate drug

a. Is the patient in pain? Cf. supra

b. Is the patient talking about anxiety? Consider use of benzodiazepine.

c. Is the patient delirious? Cf. infra.

d. Consider withdrawal syndrome if patient is a psychoactive and/or a third WHO level drug user or received continuous sedation in the last 48 hrs: test reintroduction of the drug, consider clonidine to withdraw previous treatment

REASSESSEMENT WITHIN 4 HOURS

DELIRIUM = CAM-ICI POSITIF

REFER TO THE PHYSICIAN IN CHARGE

1) Diagnose the source of delirium*

2) Choose the appropriate drug

a. Use a neuroleptic in case of agitation (RASS ≥ +2)
   -Haldol® if the patient is confused or describing hallucinations
   -Nozinan® in case of predominant anxiety or sutained RASS ≥ 3

b. Use dexmedetomidine idf neuroleptics are inefficient or proscribed

REASSESSEMENT WITHIN 6 HOURS

*Serious painful event, brain injury, fever or sepsis), hydroelectrolytic disorders, acute urinary retention, fecal impaction, analgesic-associated

SUPPLEMENTAL MATERIAL 5: DAILY CRITICAL CARE MANAGEMENT OF SYSTEMATIC PHYSICAL RESTRAINT

GROUP
RESTRICTIVE PHYSICAL RESTRAINT

DATE
From D0 to D14 __ __/__ __/____

SCHEDULE (X = mandatory; x = if needed)	AM					PM											AM						
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
PAIN/SEDATION-AGITATION/DELIRIUM ASSESSEMENTS																								
I : Assess pain using BPS: TARGET ≤ 4 Refer to the specific clinical pathway on the back of the sheet if BPS > 4.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
II : Assess agitation/sedation using RASS : TARGET -1/0/+1 (-4/-5 in case of ARDS or ICH) Refer to the specific clinical pathway on the back of the sheet if RASS ≥ +3. **Mention physical restraint session |----|**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
III : Assess delirium only if RASS ≥ - 3 using CAM-ICU **Refer to the specific clinical pathway on the back of the sheet** criteria I +II and criteria III and /or IV present - Criteria I present (Yes/No) - Criteria II present (Yes/No) - Criteria III present (Yes/No) - Criteria IVpresent (Yes/No)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY SCREEN																								
I : SAT safety screen Follow and complete the clinical pathway on the back sheet. If appropriate do SAT and go to SBT. Mention both sedatives STOPS (SAT) and RESTARTS (R) times.	ONCE A DAY BETWEEN 8AM AND NOON																							
II : SBT safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do SBT. Mention both SBT, EXTUBATION (E), and REINTUBATION (R).	ONCE A DAY BETWEEN 8AM AND NOON																							
III : EM safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do EM according to patients'status Mention both (MAP, MAA, PV, BL, MFP, MFA, walk)	ONCE A DAY BETWEEN 8AM AND NOON																							

BPS = Behavioral pain scale; RASS = Richmond Agitation-Sedation Scale; SAT= spontaneous awakening trial; SBT = spontaneous breathing trial; EM = early mobilization

SUPPLEMENTAL MATERIAL 6: CLINICAL PATHWAYS ACCORDING TO BPS, RASS AND CAM-ICU ASSESSMENTS FOR THE RESTRICTIVE PHYSICAL RESTRAINT GROUP

Clinical pathways according to BPS, RASS, and CAM-ICU assessments

SIGNIFICANT PAIN: BPS ≥ 6

REFER TO THE PHYSICIAN IN CHARGE

1) Diagnose the source of pain

Check for a serious painful event (myocardial infarction, thromboembolic event, ileus, peritonitis)

2) Choose the appropriate analgesic

a. Use the WHO analgesic scale to treat a nociceptive pain.
   First WHO level: acetaminophen and/or nefopam
   Second WHO level: dextropropoxyfen or tramadol or nalbuphin.
   Third WHO level: morphine or fentanyl or patient-controlled analgesia.

b. Use a spasmolytic intestinal drug to treat an intestinal spasm.

c. Use centrally acting muscle relaxants to treat a muscle contracture.

d. d. Use anti-inflammatory nonsteroid drugs (AINS) to treat an inflammatory pain if first and second WHO level analgesics are inefficient.

SIGNIFICANT AGITATION: RASS ≥ +2

REFER TO THE PHYSICIAN IN CHARGE

1) Physical restraint if RASS ≥ +3

2) Diagnose the source of agitation*

3) Choose the appropriate drug

a. Is the patient in pain? Cf. supra

b. Is the patient talking about anxiety? Consider use of benzodiazepine.

c. Is the patient delirious? Cf. infra.

d. Consider withdrawal syndrome if patient is a psychoactive and/or a third WHO level drug user or received continuous sedation in the last 48 hrs: test reintroduction of the drug, consider clonidine to withdraw previous treatment

REASSESSEMENT WITHIN 4 HOURS

DELIRIUM = CAM-ICI POSITIF

REFER TO THE PHYSICIAN IN CHARGE

1) Diagnose the source of delirium*

2) Choose the appropriate drug

a. Use a neuroleptic in case of agitation (RASS ≥ +2)
   -Haldol® if the patient is confused or describing hallucinations
   -Nozinan® in case of predominant anxiety or sutained RASS ≥ 3

b. Use dexmedetomidine idf neuroleptics are inefficient or proscribed

REASSESSEMENT WITHIN 6 HOURS

*Serious painful event, brain injury, fever or sepsis), hydroelectrolytic disorders, acute urinary retention, fecal impaction, analgesic-associated

SUPPLEMENTAL MATERIAL 7: STATISTICAL ANALYSIS PLAN FOR A MULTICENTER PARALLEL-GROUP OPEN LABEL RANDOMIZED CONTROLLED TRIAL

(VERSION DECEMBER 12 2023)

Table

1 ENDPOINTS

Endpoints will be compared between randomization groups (restrictive use of PR vs. systematic use of PR).

1.1 Primary endpoint

It will be the number of delirium-free or coma-free days, defined as the number of days in the first 14 days after randomization during which the patient was alive without delirium or not in coma from any cause. This endpoint will be assessed twice a day by the French validated translation of the Richmond Agitation Sedation Score (RASS) and CAM-ICU by well-trained nurses. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score > or = -3 will be assessed for delirium with the use of the CAM-ICU scale.

1.2 Secondary endpoints

1.2.1 Delirium duration until ICU discharge

This criterion is defined by the number of days on delirium until ICU discharge, the proportion of positive CAM-ICU until ICU discharge.

1.2.2 Incidence of delirium between D0 and D14

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 and D14.

1.2.3 Incidence of delirium until ICU discharge

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 until ICU discharge.

1.2.4 Agitation duration between D0 and D14

This criterion is defined by the number of days alive with agitation (RASS ≥ 2) between D0-D14.

1.2.5 Exposure to analgesic (opioids) between D0 and D14

This criterion is defined by the total cumulative dose of opiod analgesics (and subclass of opioids) between D0 and D14.

1.2.6 Exposure to propofol between D0 and D14

This criterion is defined by the total cumulative dose of propofol between D0 and D14.

1.2.7 Exposure to benzodiazepines between D0 and D14

This criterion is defined by the total cumulative dose of benzodiazepines as anxiolytic between D0 and D14.

1.2.8 Exposure to antipsychotic agents between D0 and D14

This criterion is defined by the total cumulative dose of antipsychotics agents (Haloperidol, Levomepromazine and Cyamemazine) between D0 and D14.

1.2.9 Exposure to dexmetomidine between D0 and D14

This criterion is defined by the total cumulative dose of dexemtomidine between D0 and D14

1.2.10 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

This criterion is defined by the total number of hours without mechanical ventilation between D0 and D14.

1.2.11 Patient mobility according to the visual global mobilisation score between D0 and D14

This criterion is defined by the Median of Mobilisation capacity and rate of patients > 2 on a visual scale ranging from 0 (no mobilisation) to 4 (ambulation) between D0- D14.

1.2.12 Incidence of self-extubation and device removal between D0 and D14

This criterion is defined by the rate of patients with at least one self-extubation or any device removal (Central catheter, arterial catheter or urinary catheter) between D0 and D14.

1.2.13 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

This criterion is defined by the rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel between D0-D14 (at least one ulcer of grade III or IV per patient).

1.2.14 ICU and hospital lengths of stay

This criterion is defined by the number of hospitalization day.

1.2.15 In-ICU and in-hospital mortality

This criterion is defined by the mortality rate on ICU stay and during hospitalization.

1.2.16 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

This criterion is defined by:

- The rate of patients with at D90 an altered cognitive capability defined as a MMSE (Mini Mental State Examination) ≤ 24 points
- The rate of patients with a frontal syndrome defined as a FAB (Frontal Assessment Battery at Bedside) < 15 points
- The rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder (PTSD) defined as a R-IES (Revised-Impact of events scale) ≥ 33 points
- The rate of patients with a functional disability defined as a GOS-E (Glasgow Outcome Scale – Extended) ≤ 6 points
- The rate of patients with functional independence, evaluated by the FIM (Functional Independence Measurement)

2 GENERAL CONSIDERATIONS

2.1 Flowchart

A flowchart following *Consolidated Standards of Reporting Trials (CONSORT)* standards, describing patients flow throughout the study, included and randomized, will be provided. The flowchart will specify the number of patients in each arm and describe loss of patients during the study.

2.2 Level of statistical significance

In this study, the statistical level of significance (Type I error) will be fixed at 5%.

2.3 First day of patient- follow-up (D0)

The first day of patient follow-up (D0) is the day of randomization. This day is the reference day which will be used as the initial date in the calculation of all delays.

3 STATISTICAL ANALYSIS

3.1 Descriptive analysis

The variables that will be described are as follows:

- Comorbidities/Demographic data of the included population and at ICU admission
- Treatments administred at ICU admission (Ketamine, Etomidate, Propofol and others)
- Clinical and biological data at ICU admission and from D1 to D14
- Clinical scores at ICU admission and from D1 to D14
- End-of-study data/Discharge assessment
- Clinical scores at D90

The dedicated score to assess the delirium-free and coma-free days will be described per day – morning and evening assessment. A time plot will be provided to allow a graphical description of the quality assessment between D0 and D14. Melatonin exposure will be described per day and on total, with normalization on number of days on ICU to allow patients discharged before D14 to be taken into account.

All qualitative variables will be described by their number and corresponding frequency. Quantitative variables will be described by their min and max, mean and standard deviation, median, Q1 and Q3. For each variable, the number and frequency of missing data will be reported. The description will be made for all patients and then according to the randomisation group (systematic PR vs. restrictive PR). The total number of patients and in each group will be specified. Melatonin exposure description will be also made according to the use of different devices in the medical room (i.e. earplugs, masks, natural light).

Results of descriptive analysis will be presented in tables as follows:

	Total population (N=)	Systematic PR (N=)	Restrictive PR (N=)
Quantitative variable			
	Range	Range	Range
	Median [IQR]	Median [IQR]	Median [IQR]
	Mean (SD)	Mean (SD)	Mean (SD)
	NA (n (%))	NA (n (%))	NA (n (%))
Qualitative variable			
« First modality »	% (n/N)	% (n/N)	% (n/N)
« Second modality »	% (n/N)	% (n/N)	% (n/N)

Missing	% (n/N)	% (n/N)	% (n/N)

3.2 Analysis of the primary endpoint

Analysis set

The main analysis will be in intent to treat (ITT), that is, patients will be analyzed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analyzed in the arm of management actually received.

Descriptive statistics and graphical representation

Results of CAM-ICU (Positive/Negative/Not done) will be described each day and for each evaluation, with sample size and proportion of patients in each modality, from D0 to D14, on total population and according to the randomisation group.

We will construct a variable summarizing CAM-ICU results each day (Morning CAM-ICU positive and evening CAM-ICU negative/Morning CAM-ICU negative and evening CAM-ICU positive/Both morning and evening CAM-ICU positives/Both morning and evening CAM-ICU negatives) from D0 to D14. This variable will be described with sample size and proportion of patient in each modality, from D0 to D14, on total population and according to the randomisation group.

The number of patients without coma and delirium will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The number of delirium-free and coma-free days will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made for all patients and then according to the randomisation group.

Statistical methodology

A variable corresponding to the number of delirium-free and coma-free days between D0 and D14 (primary endpoint) will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where all CAM-ICU evaluations (morning, evening or supplementary CAM-ICU evaluations) are negative. Each day, from D0 to D14, primary endpoint for ICU discharged patients will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days will be considered days of coma.

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all RASS or CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by days with coma.
- If there are non-missing data before and after the missing data and data before missing data show RASS ≥ -3 (patient not considered comatose), missing result will be imputed by days without coma.
- It will be considered that a delirium day cannot be a coma day and vice versa, meaning that in case of days with RASS ≤ -4 (patient considered comatose), and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value and in case of days with positive CAM-ICU and missing RASS, RASS results are imputed by no coma days.
- In case of missing data until D14, a last value carried forward imputation method will be performed, for both RASS and CAM-ICU

The number of coma or delirium free days between D0 and D14 will be compared between randomisation group using Student’s t-test or Wilcoxon text as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3 Analyses of secondary endpoints

3.3.1 Delirium duration until ICU discharge

Analysis set

This analysis will be performed on the sub-population of patients having at least one day of delirium between D0 and D14.

Descriptive statistics and graphical representation

The number of days with delirium (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The proportion of positive CAM-ICU until ICU discharge will be described using frequencies, on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The number of CAM-ICU performed until ICU discharge will be constructed for each patient. This variable will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

Statistical methodology

The number of days with delirium will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where at least one of the morning, evening or supplementary CAM-ICU evaluations is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value
- In case of missing data until D14, a last value carried forward imputation method will be performed

Number of days with delirium between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

The proportion of positive CAM-ICU until ICU discharge will be compared between randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test. Proportions of positive CAM-ICU will be presented with 95% confidence intervals according to the randomisation group.

The number of CAM-ICU performed until ICU discharge will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.2 Incidence of delirium between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with delirium (constructed variable, see below) will be described each day, between D0 and D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

Patients with delirium between D0 and D14 are defined as patients experiencing delirium at least one day from D0 to D14, a delirium day being a day with at least one of the morning,

evening or supplementary CAM-ICU evaluations that is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value.
- In case of missing data until D14, a last value carried forward imputation method will be performed

Rate of patients with delirium between D0 and D14 will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients with delirium between D0 and D14 with 95% confidence intervals and according to the randomisation group.

3.3.3 **Agitation duration between D0 and D14**

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The number of days with agitation (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

The number of days with agitation between D0 and D14 will be a constructed variable, indicating for each patient the total amount of days where the patient is alive with RASS ≥ 2. Imputation methods for this endpoint are as follows:

- If the patient is discharged before D14, after extubation, the remaining days are considered no agitation days.
- If the patient is discharged before D14, always in MV, the remaining days are considered agitation days.
- If the patient dies within 14 days, the number of non-surviving days are considered as no agitation days.

In case of partial missing RASS evaluation (i.e. at least one of the morning, evening or supplemental RASS evaluation is not missing), we will impute the missing RASS evaluation by the non-missing evaluation of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with days with total missing RASS evaluation, we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by coma days (i.e. RASS ≤ -4).
- In case of missing data until D14 for RASS score, a last value carried forward imputation method will be performed

The number of days with agitation between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3.4 Exposure to analgesic (opioids) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Doses of analgesic (opioids) will be described each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Total cumulative dose of analgesic (opioids) from D0 to D14 will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. Total cumulative doses of analgesic (opioids) between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.5 Exposure to propofol between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative doses of propofol from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of propofol between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.6 Exposure to benzodiazepines between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative dose of benzodiazepines from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of benzodiazepines between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.7 Exposure to antipsychotic agents between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose from D0 to D14 for each antipsychotic agent (i.e. Haloperidol, Levomepromazine and Cyamemazine) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The same description will be made for total cumulative dose of all antipsychotic agent.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of antipsychotic agents between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.8 Exposure to dexmedetomidine between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose of dexmedetomidine will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical method

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of dexmedetomidine between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.9 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The number of patients exposed to IMV will be described each day, from D0 to D14, using frequencies. The description will be made for the total population and according to the randomisation group. The same description will be made for the number of patients exposed to IMV between D0 and D14.

The total amount of hours under IMV between D0 and D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For invasive mechanical ventilation exposure, it will be considered that:

- If the patient is discharged before D14, after extubation, the remaining days are not considered as days with exposure to invasive mechanical ventilation
- If the patient is discharged before D14, always in MV, the remaining days are considered as days with MV
- If the patient is discharged before D14, not in MV, the remaining days are considered as days without MV
- If the patient dies within 14 days, the remaining days are considered as days with MV

Exposure to IMV will be compared according to the randomisation group using student's t-test or Wilcoxon as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.10 Patient mobility according to the visual global mobilisation score between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The visual global mobilisation score will be descripted each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The visual global mobilisation score will be also descripted for the total D0-D14 period, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The rate of patients with global mobilisation score > 2 will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

Boxplots of the visual global mobilisation score from D0 to D14 will be realized to allow graphical representation of patient mobility.

Statistical methodology

There will be no methods for replacing missing data. The median of the visual mobilisation score on the D0-D14 period will be firstly normalized by the number of days under ICU hospitalization, to allow discharge from ICU or death before D14 to be taken into account. Normalized visual mobilisation score on the D0-D14 period will be compared between

randomisation group using Wilcoxon test. Results will be presented using median and p-value of the test.

3.3.11 Incidence of self-extubation and device removal between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patient experiencing self-extubation will be described for each device (self-extubation, removal of central catheter, arterial catheter or urinary catheter), each day for D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The same description will be realized for self-extubation or any device removal and for any device removal only.

Statistical methodology

The proportion of patients with self-extubation or any device removal will be compared between randomisation groups using chi-squared or Fisher test as appropriate. The same comparison between randomisation groups will be made for patients experiencing self-extubation only and for patients experiencing any device removal only. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.12 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patients with skin lesions will be described for each skin lesion (wrist, heel, sacrum, other), each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

The proportion of patients with at least one of the four types of skin lesions (wrist, heel, sacrum, other) will be described, each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

Statistical methodology

The proportion of patients with wrist lesions, the proportion of patients with heel lesions, the proportion of patients with sacrum lesions, and the proportion of patients with other skin lesions between D0 and D14 and according to the randomisation group will be analysed individually using chi-squared or Fisher test as appropriate. Results will be presented using p-value of the tests as well as proportion of patients with each lesion with their 95% interval confidence and according to the randomisation group.

The same analysis will be realized for patients having at least one of the four types of skin lesion (wrist, heel, sacrum, other) between D0 and D14 using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.13 ICU and hospital lengths of stay

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The ICU length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The hospital length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodologyFor patients dying within 14 days, it will be considered that they stayed in ICU and hospital from ICU admission to date of death and from hospital admission to date of death respectively. In case of missing date for ICU discharge or hospital discharge outside patients who died within 14 days, the date of discharge from ICU/hospital will be imputed by the date of the patient's last news.

ICU length of stay and hospital length of stay will be analysed between according to randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.14 In-ICU and in-hospital mortality

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The proportion of dead patients will be described each day, from D0 to D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

To allow lost-to-follow up patients to be taken into account, a Kaplan-Meier model will be realized, the event of interest being in-ICU death or in-hospital death. We will perform a log rank test to compare survival distributions according to the randomisation group. Results will be presented using p value of the log rank test, as well as proportion of death at day 90 between randomisation groups with their 95% interval confidence and according to the randomisation group.

3.3.15 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with altered cognitive capabilities at D90, the rate of patients with a frontal syndrome at D90, the rate of patients with a possible diagnosis of PTSD, the rate of patients with a functional disability at D90 and the rate of patients with a functional independence at D90 will be described using frequencies. These descriptions will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no imputation for missing data. Each individual endpoint will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test as well as proportion of patients with altered cognitive

capabilities at D90, proportion of patients with a frontal syndrome at D90, proportion of patients with a possible diagnosis of PTSD, proportion of patients with a functional at D90 and proportion of patients with a functional independence at D90. Each proportion will be provided with their 95% interval confidence and according to the randomisation group.

3.3.16 Center effect, age group effect and presence of coma at beginning of IMV effect

The center effect will be assessed by testing interaction between trial arm and the center in a linear regression modelling the number of delirium-free and coma-free days between D0 and D14. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of IMV. Results will be presented using coefficients of the linear regression with 95% confidence intervals as well as p-value of the tests. In case if significant interaction, a sub-group analysis will be performed.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2.

3.4 Sensitivity analysis

3.4.1 Number of days lived without coma and without delirium for patients leaving ICU before D14

This analysis will consist of a multivariate linear regression predicting the number of days lived without coma and without delirium in the sub-population of patients leaving ICU before D14, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2. Missing values for MV exposure will be imputed using same methodologies as described in §3.3.9. There will be no imputation for sedation time.

3.4.2 Physical restraint exposure

A sensitivity analysis will be performed on primary endpoint for patients whose exposure to either restrictive or systematic RA has been fully respected over the 14 days according to the

predefined rules. In addition, an analysis will be carried out on patients who have had no change in their exposure to RA during the 14 days or until discharge from intensive care after extubation.

3.4.3 Sedative exposure at intubation at D0

Sensitivity analysis for the primary endpoint will be performed on the sub-population of patients exposed to sedative agents at intubation at D0.

3.5 Subgroup analysis

3.5.1 Center effect, age group effect and presence of coma at beginning of IMV effect

In case of significant interaction for analyses described in §3.3.16, a sub-group analysis will be performed for the prediction of number of delirium-free and coma-free days between D0 and D14. An ANOVA will be used for comparison of number of delirium-free and coma-free days from D0 to D14 between centres. We will use Student's t-test test or Wilcoxon test as appropriate to compare number of delirium-free and coma-free days from D0 to D14 between age groups and according to presence of coma at beginning of IMV. Results will be presented using mean or median as appropriate and p-values of the test.

3.5.2 Covid patients

A subgroup analysis will be performed on patients exposed to COVID for the comparison of number of delirium-free and coma-free days between D0 and D14 and according to COVID exposure. We will use Sudent's t-test or Fisher test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

4 SOFTWARE

Statistical analyses will be made using R v. 4.2.1 or later (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/), or SAS Version 9.4 or later (SAS Institute Inc., Cary,NC).

Restrictive use of Restraints and Delirium Duration in the Intensive Care Unit (R2D2-ICU): Statistical Analysis Plan for a Multicentre Parallel-group Open Label Randomized Controlled Trial

Table

1! Endpoints

Endpoints will be compared between randomization groups (restrictive use of PR vs. systematic use of PR).

1.1! Primary endpoint

It will be the number of delirium-free or coma-free days, defined as the number of days in the first 14 days after randomization during which the patient was alive without delirium or not in coma from any cause. This endpoint will be assessed twice a day by the French validated translation of the Richmond Agitation Sedation Score (RASS) and CAM-ICU by well-trained nurses. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score > or = -3 will be assessed for delirium with the use of the CAM-ICU scale.

1.2! Secondary endpoints

1.2.1! Delirium duration until ICU discharge

This criterion is defined by the number of days on delirium until ICU discharge, the proportion of positive CAM-ICU until ICU discharge.

1.2.2! Incidence of delirium between D0 and D14

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 and D14.

1.2.3! Incidence of delirium until ICU discharge

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 until ICU discharge.

1.2.4! Agitation duration between D0 and D14

This criterion is defined by the number of days alive with agitation (RASS ≥ 2) between D0-D14.

1.2.5! Exposure to analgesic (opioids) between D0 and D14

This criterion is defined by the total cumulative dose of opiod analgesics (and subclass of opioids) between D0 and D14.

1.2.6! Exposure to propofol between D0 and D14

This criterion is defined by the total cumulative dose of propofol between D0 and D14.

1.2.7! Exposure to benzodiazepines between D0 and D14

This criterion is defined by the total cumulative dose of benzodiazepines as anxiolytic between D0 and D14.

1.2.8! Exposure to antipsychotic agents between D0 and D14

This criterion is defined by the total cumulative dose of antipsychotics agents (Haloperidol, Levomepromazine and Cyamemazine) between D0 and D14.

1.2.9! Exposure to dexmetomidine between D0 and D14

This criterion is defined by the total cumulative dose of dexemtomidine between D0 and D14

1.2.10! Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

This criterion is defined by the total number of hours without mechanical ventilation between D0 and D14.

1.2.11! Patient mobility according to the visual global mobilisation score between D0 and D14

This criterion is defined by the Median of Mobilisation capacity and rate of patients > 2 on a visual scale ranging from 0 (no mobilisation) to 4 (ambulation) between D0- D14.

1.2.12! Incidence of self-extubation and device removal between D0 and D14

This criterion is defined by the rate of patients with at least one self-extubation or any device removal (Central catheter, arterial catheter or urinary catheter) between D0 and D14.

1.2.13! Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

This criterion is defined by the rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel between D0-D14 (at least one ulcer of grade III or IV per patient).

1.2.14! ICU and hospital lengths of stay

This criterion is defined by the number of hospitalization day.

1.2.15! In-ICU and in-hospital mortality

This criterion is defined by the mortality rate on ICU stay and during hospitalization.

1.2.16! Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

This criterion is defined by:

- The rate of patients with at D90 an altered cognitive capability defined as a MMSE (Mini Mental State Examination) ≤ 24 points
- The rate of patients with a frontal syndrome defined as a FAB (Frontal Assessment Battery at Bedside) < 15 points
- The rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder (PTSD) defined as a R-IES (Revised-Impact of events scale) ≥ 33 points
- The rate of patients with a functional disability defined as a GOS-E (Glasgow Outcome Scale – Extended) ≤ 6 points
- The rate of patients with functional independence, evaluated by the FIM (Functional Independence Measurement)

2! General considerations

2.1! Flowchart

A flowchart following *Consolidated Standards of Reporting Trials (CONSORT)* standards, describing patients flow throughout the study, included and randomized, will be provided. The flowchart will specify the number of patients in each arm and describe loss of patients during the study.

2.2! Level of statistical significance

In this study, the statistical level of significance (Type I error) will be fixed at 5%.

2.3! First day of patient- follow-up (D0)

The first day of patient follow-up (D0) is the day of randomization. This day is the reference day which will be used as the initial date in the calculation of all delays.

3! Statistical analysis

3.1! Descriptive analysis

The variables that will be described are as follows:

- Comorbidities/Demographic data of the included population and at ICU admission
- Treatments administred at ICU admission (Ketamine, Etomidate, Propofol and others)
- Clinical and biological data at ICU admission and from D1 to D14
- Clinical scores at ICU admission and from D1 to D14

- End-of-study data/Discharge assessment
- Clinical scores at D90

The dedicated score to assess the delirium-free and coma-free days will be described per day – morning and evening assessment. A time plot will be provided to allow a graphical description of the quality assessment between D0 and D14. Melatonin exposure will be described per day and on total, with normalization on number of days on ICU to allow patients discharged before D14 to be taken into account.

All qualitative variables will be described by their number and corresponding frequency. Quantitative variables will be described by their min and max, mean and standard deviation, median, Q1 and Q3. For each variable, the number and frequency of missing data will be reported.

The description will be made for all patients and then according to the randomisation group (systematic PR vs. restrictive PR). The total number of patients and in each group will be specified. Melatonin exposure description will be also made according to the use of different devices in the medical room (i.e. earplugs, masks, natural light).

Results of descriptive analysis will be presented in tables as follows:

	Total population (N=)	Systematic PR (N=)	Restrictive PR (N=)
Quantitative variable			
	Range	Range	Range
	Median [IQR]	Median [IQR]	Median [IQR]
	Mean (SD)	Mean (SD)	Mean (SD)
	NA (n (%))	NA (n (%))	NA (n (%))
Qualitative variable			
« First modality »	% (n/N)	% (n/N)	% (n/N)
« Second modality »	% (n/N)	% (n/N)	% (n/N)
Missing	% (n/N)	% (n/N)	% (n/N)

3.2! Analysis of the primary endpoint

Analysis set

The main analysis will be in intent to treat (ITT), that is, patients will be analyzed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analyzed in the arm of management actually received.

Descriptive statistics and graphical representation

Results of CAM-ICU (Positive/Negative/Not done) will be described each day and for each evaluation, with sample size and proportion of patients in each modality, from D0 to D14, on total population and according to the randomisation group.

We will construct a variable summarizing CAM-ICU results each day (Morning CAM-ICU positive and evening CAM-ICU negative/Morning CAM-ICU negative and evening CAM-ICU positive/Both morning and evening CAM-ICU positives/Both morning and evening CAM-ICU negatives) from D0 to D14. This variable will be described with sample size and proportion of patient in each modality, from D0 to D14, on total population and according to the randomisation group.

The number of patients without coma and delirium will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The number of delirium-free and coma-free days will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made for all patients and then according to the randomisation group.

Statistical methodology

A variable corresponding to the number of delirium-free and coma-free days between D0 and D14 (primary endpoint) will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where all CAM-ICU evaluations (morning, evening or supplementary CAM-ICU evaluations) are negative. Each day, from D0 to D14, primary endpoint for ICU discharged patients will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days will be considered days of coma.

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all RASS or CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by days with coma.
- If there are non-missing data before and after the missing data and data before missing data show RASS ≥ -3 (patient not considered comatose), missing result will be imputed by days without coma.
- It will be considered that a delirium day cannot be a coma day and vice versa, meaning that in case of days with RASS ≤ -4 (patient considered comatose), and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value and in case of days with positive CAM-ICU and missing RASS, RASS results are imputed by no coma days.
- In case of missing data until D14, a last value carried forward imputation method will be performed, for both RASS and CAM-ICU

The number of coma or delirium free days between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon text as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3! Analyses of secondary endpoints

3.3.1! Delirium duration until ICU discharge

Analysis set!

This analysis will be performed on the sub-population of patients having at least one day of delirium between D0 and D14.

Descriptive statistics and graphical representation!

The number of days with delirium (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The proportion of positive CAM-ICU until ICU discharge will be described using frequencies, on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The number of CAM-ICU performed until ICU discharge will be constructed for each patient. This variable will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

Statistical methodology!

The number of days with delirium will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where at least one of the morning, evening or supplementary CAM-ICU evaluations is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value
- In case of missing data until D14, a last value carried forward imputation method will be performed

Number of days with delirium between D0 and D14 will be compared between randomisation group using Student’s t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

The proportion of positive CAM-ICU until ICU discharge will be compared between randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test. Proportions of positive CAM-ICU will be presented with 95% confidence intervals according to the randomisation group.

The number of CAM-ICU performed until ICU discharge will be compared between randomisation group using Student’s t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.2 Incidence of delirium between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with delirium (constructed variable, see below) will be described each day, between D0 and D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

Patients with delirium between D0 and D14 are defined as patients experiencing delirium at least one day from D0 to D14, a delirium day being a day with at least one of the morning, evening or supplementary CAM-ICU evaluations that is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.

- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value.
- In case of missing data until D14, a last value carried forward imputation method will be performed

Rate of patients with delirium between D0 and D14 will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients with delirium between D0 and D14 with 95% confidence intervals and according to the randomisation group.

3.3.3! Agitation duration between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The number of days with agitation (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

The number of days with agitation between D0 and D14 will be a constructed variable, indicating for each patient the total amount of days where the patient is alive with RASS ≥ 2. Imputation methods for this endpoint are as follows:

- If the patient is discharged before D14, after extubation, the remaining days are considered no agitation days.
- If the patient is discharged before D14, always in MV, the remaining days are considered agitation days.

- If the patient dies within 14 days, the number of non-surviving days are considered as no agitation days.

In case of partial missing RASS evaluation (i.e. at least one of the morning, evening or supplemental RASS evaluation is not missing), we will impute the missing RASS evaluation by the non-missing evaluation of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with days with total missing RASS evaluation, we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by coma days (i.e. RASS ≤ -4).
- In case of missing data until D14 for RASS score, a last value carried forward imputation method will be performed

The number of days with agitation between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3.4! Exposure to analgesic (opioids) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation!

Doses of analgesic (opioids) will be described each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Total cumulative dose of analgesic (opioids) from D0 to D14 will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology!

There will be no methods for replacing missing data. Total cumulative doses of analgesic (opioids) between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.5! Exposure to propofol between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative doses of propofol from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of propofol between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.6! Exposure to benzodiazepines between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative dose of benzodiazepines from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of benzodiazepines between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.7! Exposure to antipsychotic agents between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose from D0 to D14 for each antipsychotic agent (i.e. Haloperidol, Levomepromazine and Cyamemazine) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The same description will be made for total cumulative dose of all antipsychotic agent.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of antipsychotic agents between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.8! Exposure to dexmedetomidine between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose of dexmedetomidine will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical method

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of dexmedetomidine between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.9! Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The number of patients exposed to IMV will be described each day, from D0 to D14, using frequencies. The description will be made for the total population and according to the randomisation group. The same description will be made for the number of patients exposed to IMV between D0 and D14.

The total amount of hours under IMV between D0 and D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For invasive mechanical ventilation exposure, it will be considered that:

- If the patient is discharged before D14, after extubation, the remaining days are not considered as days with exposure to invasive mechanical ventilation

- If the patient is discharged before D14, always in MV, the remaining days are considered as days with MV
- If the patient is discharged before D14, not in MV, the remaining days are considered as days without MV
- If the patient dies within 14 days, the remaining days are considered as days with MV

Exposure to IMV will be compared according to the randomisation group using student's t-test or Wilcoxon as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.10! Patient mobility according to the visual global mobilisation score between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The visual global mobilisation score will be descripted each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The visual global mobilisation score will be also descripted for the total D0-D14 period, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The rate of patients with global mobilisation score > 2 will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

Boxplots of the visual global mobilisation score from D0 to D14 will be realized to allow graphical representation of patient mobility.

Statistical methodology!

There will be no methods for replacing missing data. The median of the visual mobilisation score on the D0-D14 period will be firstly normalized by the number of days under ICU hospitalization, to allow discharge from ICU or death before D14 to be taken into account. Normalized visual mobilisation score on the D0-D14 period will be compared

between randomisation group using Wilcoxon test. Results will be presented using median and p-value of the test.

3.3.11! Incidence of self-extubation and device removal between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation!

The proportion of patient experiencing self-extubation will be described for each device (self-extubation, removal of central catheter, arterial catheter or urinary catheter), each day for D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The same description will be realized for self-extubation or any device removal and for any device removal only.

Statistical methodology!

The proportion of patients with self-extubation or any device removal will be compared between randomisation groups using chi-squared or Fisher test as appropriate. The same comparison between randomisation groups will be made for patients experiencing self-extubation only and for patients experiencing any device removal only. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.12! Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

Analysis set!

This analysis will be performed on the total population.

Descriptive statistics and graphical representation!

The proportion of patients with skin lesions will be described for each skin lesion (wrist, heel, sacrum, other), each day from D0 to D14, using frequencies. This description will

be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

The proportion of patients with at least one of the four types of skin lesions (wrist, heel, sacrum, other) will be described, each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

Statistical methodology

The proportion of patients with wrist lesions, the proportion of patients with heel lesions, the proportion of patients with sacrum lesions, and the proportion of patients with other skin lesions between D0 and D14 and according to the randomisation group will be analysed individually using chi-squared or Fisher test as appropriate. Results will be presented using p-value of the tests as well as proportion of patients with each lesion with their 95% interval confidence and according to the randomisation group.

The same analysis will be realized for patients having at least one of the four types of skin lesion (wrist, heel, sacrum, other) between D0 and D14 using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.13 ICU and hospital lengths of stay

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The ICU length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The hospital length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodologyFor patients dying within 14 days, it will be considered that they stayed in ICU and hospital from ICU admission to date of death and from hospital admission to date of death respectively. In case of missing date for ICU discharge or hospital discharge outside patients who died within 14 days, the date of discharge from ICU/hospital will be imputed by the date of the patient's last news.

ICU length of stay and hospital length of stay will be analysed between according to randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.14! In-ICU and in-hospital mortality

Analysis set!

This analysis will be performed on the total population

Descriptive statistics and graphical representation!

The proportion of dead patients will be described each day, from D0 to D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology!

To allow lost-to-follow up patients to be taken into account, a Kaplan-Meier model will be realized, the event of interest being in-ICU death or in-hospital death. We will perform a log rank test to compare survival distributions according to the randomisation group. Results will be presented using p value of the log rank test, as well as proportion of death at day 90 between randomisation groups with their 95% interval confidence and according to the randomisation group.

3.3.15! Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with altered cognitive capabilities at D90, the rate of patients with a frontal syndrome at D90, the rate of patients with a possible diagnosis of PTSD, the rate of patients with a functional disability at D90 and the rate of patients with a functional independence at D90 will be described using frequencies. These descriptions will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no imputation for missing data. Each individual endpoint will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test as well as proportion of patients with altered cognitive capabilities at D90, proportion of patients with a frontal syndrome at D90, proportion of patients with a possible diagnosis of PTSD, proportion of patients with a functional at D90 and proportion of patients with a functional independence at D90. Each proportion will be provided with their 95% interval confidence and according to the randomisation group.

3.3.16 Center effect, age group effect and presence of coma at beginning of IMV effect

The center effect will be assessed by testing interaction between trial arm and the center in a linear regression modelling the number of delirium-free and coma-free days between D0 and D14. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of IMV. Results will be presented using coefficients of the linear regression with 95% confidence intervals as well as p-value of the tests. In case if significant interaction, a sub-group analysis will be performed.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2.

3.4 Sensitivity analysis

3.4.1! Number of days lived without coma and without delirium for patients leaving ICU before D14

This analysis will consist of a multivariate linear regression predicting the number of days lived without coma and without delirium in the sub-population of patients leaving ICU before D14, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2. Missing values for MV exposure will be imputed using same methodologies as described in §3.3.9. There will be no imputation for sedation time.

3.4.2! Physical restraint exposure

A sensitivity analysis will be performed on primary endpoint for patients whose exposure to either restrictive or systematic RA has been fully respected over the 14 days according to the predefined rules. In addition, an analysis will be carried out on patients who have had no change in their exposure to RA during the 14 days or until discharge from intensive care after extubation.

3.4.3! Sedative exposure at intubation at D0

Sensitivity analysis for the primary endpoint will be performed on the sub-population of patients exposed to sedative agents at intubation at D0.

3.5! Subgroup analysis

3.5.1! Center effect, age group effect and presence of coma at beginning of IMV effect

In case of significant interaction for analyses described in §3.3.16, a sub-group analysis will be performed for the prediction of number of delirium-free and coma-free days between D0 and D14. An ANOVA will be used for comparison of number of delirium-free and coma-free days from D0 to D14 between centres. We will use Student's t-test test or Wilcoxon test as appropriate to compare number of delirium-free and coma-free days from

D0 to D14 between age groups and according to presence of coma at beginning of IMV. Results will be presented using mean or median as appropriate and p-values of the test.

3.5.2! Covid patients

A subgroup analysis will be performed on patients exposed to COVID for the comparison of number of delirium-free and coma-free days between D0 and D14 and according to COVID exposure. We will use Sudent's t-test or Fisher test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

4! Software

Statistical analyses will be made using R v. 4.2.1 or later (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/), or SAS Version 9.4 or later (SAS Institute Inc., Cary,NC).

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Restrictive use of Restraints and Delirium Duration in the Intensive Care Unit (R2D2-ICU): Protocol for a Multicentre Parallel-group Open Label Randomized Controlled Trial

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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

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ABSTRACT

Introduction Physical restraint (PR) is prescribed in patients receiving invasive mechanical ventilation in the intensive care unit (ICU) to avoid unplanned removal of medical devices. However, it is associated with an increased risk of delirium. We hypothesise that a restrictive use of PR, as compared to a systematic use, could reduce the duration of delirium in ICU patients receiving invasive mechanical ventilation.

Methods and analysis The Restrictive use of Restraints and Delirium Duration in ICU (R2D2-ICU) study is a national multicentric, parallel group, randomized (1:1) open label, controlled, superiority trial which will be conducted in 10 ICUs. A total of 422 adult patients requiring invasive mechanical ventilation for an expected duration of at least 48 hours and eligible to prescription of PR will be randomly allocated within 6 hours from intubation to either the restrictive PR use group or the systematic PR use group, until day 14, ICU discharge or death, whichever comes first. In both groups, PR will consist of the use of wrist straps. The primary endpoint will be delirium or coma-free days, defined as the number of days spent alive in the ICU without coma or delirium within the first 14 days after randomisation. Delirium will be assessed using the CAM-ICU twice daily. Key secondary endpoints will encompass agitation episodes, opioid, propofol, benzodiazepine, and antipsychotic drug exposure during the 14-day intervention period, along with a core outcome set of measures evaluated 90 days post-randomization.

Ethics and dissemination The R2D2-ICU study has been approved by the Comité de Protection des Personnes (CPP) ILE DE FRANCE III – PARIS (CPP19.09.06.37521) on 06/10/2019). Participant recruitment started on January 25th, 2021. Results will be published in international peer-reviewed medical journals and presented at conferences.

Trial registration number NCT05248035, first posted on February 18th, 2020.

STRENGTHS AND LIMITATIONS

- R2D2-ICU is the first large multicentre randomized controlled trial evaluating the impact of physical restraint on the duration of delirium among mechanically ventilated patients in the intensive care unit (ICU).
- The R2D2-ICU trial evaluates a clinically relevant primary outcome, i.e., the number of delirium-free and coma-free days within the first 14 days after randomisation.
- A follow-up at 90 days will be performed with a core outcome set of secondary measures.
- Due to the open-label design of the trial, we will standardize the delirium assessment and management in both groups according to international guidelines.

INTRODUCTION

Background and rationale

The application of physical restraint (PR) within intensive care units (ICUs) has been a customary practice aimed at ensuring patient safety and averting the inadvertent removal of medical devices. However, studies have revealed substantial variability in the prevalence of PR use, with rates spanning from 0% to 100% in European ICUs [1]. Patients subjected to PR were more likely to be ventilated, sedated, and managed in larger units with lower nurse-to-patient ratios.

Interestingly, only a minority of ICUs possessed a written protocol for PR use, underscoring the absence of standardized guidelines in this field . In a randomised trial of protocolised sedation, PR was utilised in 76% of patients for a median duration of 4 days [4]. Additionally, a survey in French centres disclosed that PR was employed in over 50% of mechanically ventilated patients in 82% of ICUs, with a lack of written local procedures in the majority of cases [5].

The American guidelines on pain, agitation, and delirium management do not give specific recommendations for PR use [6,7]. In a prospective study conducted in 51 ICUs in Canada, treatment characteristics seemed to predict PR use (higher daily doses of benzodiazepines and opioids, antipsychotic drugs, and agitation), as opposed to patient or ICU characteristics [8].

Despite the commonplace application of PR, its benefits in critically ill patients remain unestablished, and it may even be deleterious, by causing injury, agitation, and psychological distress for patients and families. PR has been linked to adverse psychological effects, including stressful memories for survivors of critical illness [9]. Moreover, its complex association with brain dysfunction, manifested as agitation and/or delirium, raises concerns. While PR is intended to mitigate the potential risks associated with agitation, it appears to favour the development of delirium [10]. In a previous study, the risk of use of PR was increased in patients with delirium or coma, in patients who could not communicate verbally, and in patients receiving psychoactive or sedative drugs [3].

Delirium, defined as a disturbance in attention and awareness developing over a short period of time, is common occurrence in critically ill patients receiving invasive mechanical ventilation. It is associated

with poor outcomes, including higher morbidity and mortality [11], and long term cognitive impairment in survivors [12]. Recent research emphasizes the need to better understand delirium mechanistically to facilitate prevention and treatment [13]. In this context, PR may represent a modifiable risk factor for delirium in ICU patients [14,15]. The number of days without delirium in the ICU is significantly associated with both short-term mortality and long-term cognitive impairment, suggesting the potential importance of addressing PR practices in the ICU to improve patient outcomes.

Hypothesis

We hypothesize that a restrictive use of PR, as compared to a systematic use, could reduce the duration of coma and delirium among patients receiving invasive mechanical ventilation (MV) in the ICU.

Objectives

Study objectives and associated endpoints are presented in **Box 1**. The primary objective is to assess whether a restrictive use of PR, as compared to a systematic use, decreases delirium duration during the first 14 days after randomization. The 15 secondary objectives are presented in the **Box 1.**

Box 1 Study objectives and associated endpoints

Primary objective	**Primary endpoint**
To assess whether a restrictive use of PR, in comparison to a systematic use, decreases delirium duration during the first 14 days after randomization.	Delirium or coma-free days, defined by the number of days alive without delirium (measured by CAM-ICU) or coma (measured by RASS) during the first 14 days (D14) after randomization (D0).
Secondary objectives	**Secondary endpoints**
To evaluate the effect of restrictive use of PR between D0 and D14 on: ➢ Incidence of delirium ➢ Agitation duration ➢ Exposure to opioids ➢ Exposure to propofol ➢ Exposure to benzodiazepines ➢ Exposure to antipsychotic agents ➢ Exposure to dexmedetomidine ➢ Exposure to MV ➢ Patient mobility according to the visual mobilisation score ➢ Incidence of self-extubation and device removal ➢ Skin lesions occurrence	➢ percentage of patients with at least one day of delirium (positive CAM-ICU) between D0-D14 ➢ Number of days alive with agitation (RASS score ≥ +2) between D0-D14 ➢ Total cumulative dose of opioids infusion between D0-D14 ➢ Total cumulative dose of propofol infusion between D0-D14 ➢ Total cumulative dose of benzodiazepines infusion between D0-D14 ➢ Total cumulative dose of antipsychotics infusion between D0-D14 ➢ Total cumulative dose of dexmedetomidine infusion between D0-D14 ➢ Invasive mechanical ventilation-free hours between D0-D14 ➢ Median of mobilisation capacity and rate of patients >2 on a visual scale (SOMS) ranging from 0 (no mobilisation) to 4 (ambulation) between D0-D14 ➢ Rate of patients with at least one self-extubation or any device removal between D0-D14 ➢ Rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel (at least one ulcer of grade III or IV per patient) between D0-D14
To evaluate the effect of restrictive use of PR until ICU Discharge on: ➢ Delirium duration until ICU discharge: Patients will be considered "ready for discharge" as soon as all clinical conditions for ICU discharge will be fulfilled ➢ ICU and hospital lengths of stay ➢ In-ICU and in-hospital mortality	➢ Number of days on delirium until ICU discharge ➢ Number of days of ICU stay and of hospital stay [up to D90] ➢ Death rate during ICU stay and hospital stay [up to D90]
To evaluate the effect of restrictive use of PR at D90 (after inclusion) on the global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD)	➢ Rate of patients with altered cognitive capabilities defined as a score on the Mini Mental State Examination ≤ 24 points ➢ Rate of patients with a frontal syndrome defined as a score on the FAB < 15 points ➢ Rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder defined as a score on the IES-R ≥ 33 points ➢ Rate of patients with a functional disability, defined as a score on the GOS-E ≤ 6 points ➢ Functional independence status (yes or no) evaluated on the FIM scale

CAM-ICU: Confusion Assessment Method for Intensive Care Unit; D: Day; FIM Functional Independence Measurement; FAB: Frontal Assessment Battery; GOS-E Glasgow Outcome Scale-Extended; IESR: Impact of Events Scale-Revised; MV: Mechanical Ventilation; RASS Richmond Agitation Sedation Scale.

METHODS AND ANALYSIS

Design overview

The R2D2-ICU study is an investigator-initiated, national multicentric, superiority, open label parallel-group, comparative controlled randomized trial, in which patients being on invasive MV in the ICU for a duration inferior to 6 hours are allocated in a 1:1 ratio to restrictive PR use group (intervention group) or to systematic PR use group (control group). The trial design is summarised in **table 1** and in **figure 1**. We report the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials statement (**supplementary material 1**) [16]. The selection of a parallel group design, randomised with two interventions, one of which includes systematic PR, allows for the elimination of service-specific practices, and focuses on patient-centred considerations. The practice guidelines outlined in the protocol for each group will facilitate standardised management, thereby minimising the risk of cross-contamination. 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.

Patient inclusion and randomization will be conducted either by the principal investigator or by a physician representing the investigator. Patient eligibility will be assessed in accordance with the predefined inclusion and exclusion criteria. 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.

Each centre will maintain a screening log for all eligible patients. The use of physical restraint will involve the use of wrist straps, precluding a blind investigation of group assignments. The observation period for patients will extend from the time of inclusion until their discharge from the ICU or until their demise, with a specific follow-up consultation scheduled at day 90 for all surviving patients.

Table 1. Summary study data collected

Timepoints	Screening D0	Randomisation D0	D1 to D14	Discharge	D90
Description of timepoints	Within 6 hours after beginning of invasive MV		0 to 14	Day of ICU and hospital discharge	90 days after randomization
Eligibility screen	X	X			
Informed consent*		X			
SAPS2	X	X			
SOFA	X	X			
Admission variables		x			
Demographics		x			
Comorbid conditions		x			
Drug/alcohol consumption		X			
Benzodiazepine treatment		X			
Cognitive impairment		X			
Braden scale		X			
BPS		X	X		
SARS-CoV-2 status	X				
Main reason of IMV		X			
Outcome variables					
RASS (twice a day)		X	X		
CAM-ICU (twice a day)		X	X		
Sedatives (propofol, benzodiazepines, and dexmedetomidine)			X		
Opioids			X		
Antipsychotics			X		
Agitation					
Self-extubation			X		
Accidental removal of medical devices			X		
Mobilization by visual scale			X		
Skin lesions			X		
Length of stay (ICU and Hospital)			X	X	X
Vital status			X	X	X
Follow-up consultation (mRS, MRC, MMS-E, FAB, IES-R, GOS-E, FIM, IPREA scales)					X

MV Mechanical ventilation; RASS Richmond Agitation Sedation Scale; CAM-ICU Confusion Assessment Method for the ICU; MMSE Mini Mental State Evaluation; FAB Frontal Assessment Battery; IES-R Impact of Events Scale-revised; IPREA Inconforts des Patients de REAnimation; GOS-E Glasgow Outcome Scale-Extended; FIM Functional Independence Measure; MRC Medical Research Council Scale; ICU Intensive Care Unit; SAPS2 Simplified Acute Physiology Score 2; SOFA Sequential Organ Failure Assessment; BPS behavioral pain scale; MV mechanical ventilation.

* Not mandatory, emergency inclusion is authorized by the French authorities. In case of emergency inclusion, close relative and/or patient written informed consents will be collected as soon as possible.

Interventions

For all patients, PR will consist of the use of wrists straps. The restrictive or systematic strategies will be applied until one of the following events occur, whichever comes first: a) day 14 in ICU; b) ready for "ICU discharge" (Patients will be considered "ready for discharge" as soon as all clinical conditions for ICU discharge will be fulfilled (i.e., no more need for vital-organ support, and no more need for central or arterial catheter); c) death before day 14. 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 for details).

Intervention group

In the restrictive PR use group, patients will be subjected to PR only in case of severe agitation, defined by a RASS score ≥ +3 on any given day between day 0 and day 14.

Control group

In the systematic PR use group, patients will be systematically subjected to PR, which will be re-evaluated every day every day between day 0 and day 14. The removal of PR will be allowed when patients meet any of the following criteria: 1) Awake without delirium, defined by a RASS > -4 and a negative CAM-ICU; 2) Extubated without delirium, defined by the absence of invasive MV and a negative CAM-ICU. The PR will be resumed in case of severe agitation, defined by a RASS ≥ +3 on any given day between day 0 and day 14, irrespective of the need for invasive MV.

Study setting and population

Patients will be prospectively recruited among patients admitted in 10 French ICUs. Patients will be considered eligible for enrolment if they fulfil the inclusion criteria and none of the exclusion criteria, as defined in **Box 2**. A flow diagram of the R2D2-ICU trial is presented in **figure 1**.

Box 2 Eligibility criteria

Inclusion criteria

- ✓ Adult ≥ 18 years
- ✓ Invasive mechanical ventilation expected for at least ≥ 48 hours
- ✓ Invasive mechanical ventilation in the ICU for a duration inferior to 6 hours
- ✓ Eligible to physical restraint prescription*

Exclusion criteria

- ✓ Documented delirium prior to ICU admission according to the CAM-ICU
- ✓ History of dementia (Mini mental test < 24)
- ✓ Alcohol withdrawal syndrome expected
- ✓ Admission for any neurological disease including post-cardiopulmonary resuscitation (cardiac arrest, stroke, traumatic brain injury, meningoencephalitis, and status epilepticus)
- ✓ Serious auditory or visual disorders
- ✓ Unable to understand French
- ✓ Pregnant or lactating women
- ✓ SAPS II > 65 points at screening
- ✓ Do-not-resuscitate orders
- ✓ No affiliation to a social security regime (beneficiary or assignee)
- ✓ Patient or person of confidence (if present at the time of inclusion) opposing the patient's participation in research
- ✓ Patient already involved in another interventional clinical research whose main objective is related to delirium

ICU: Intensive Care Unit; CAM ICU Confusion Method Assessment in the ICU; SAPS2: Simplified Acute Physiology Score 2.

*Not already restrained because of a previous written medical prescription.

Outcomes

Primary endpoint

The primary endpoint is delirium or coma-free days, defined by the number of days alive without delirium (measured by CAM-ICU) or coma (measured by RASS) during the first 14 days after randomization. Brain dysfunction in the ICU, i.e., delirium or coma, is serious event in critically ill patients that is associated with prolonged hospital stays, costs, increased mortality, and cognitive impairment in survivors. In this regard, the number of days alive without delirium or coma in the ICU has emerged as a clinically relevant endpoint in critical care trials [17,18]. Moreover, duration of delirium in the ICU is associated with important patient-centred outcomes, including worse global cognition and executive function at 12 months following ICU discharge [19].

This endpoint will be assessed twice daily if needed according to patients' clinical status by the French validated translation of the Richmond Agitation Sedation Score (RASS) [20] and CAM-ICU [21] by well-trained nurses as recommended by the clinical practice guidelines for Pain, Agitation, and Delirium in ICU patients. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score $\geq$ -3 will be assessed for delirium with the use of the CAM-ICU scale **(see supplemental material 2).**

The American guidelines on pain, agitation, and delirium management recommend [6,7]: 1/ the use of sedation scales to assess arousal level; 2/ if patients are assessable, the use of validated tools to assess for delirium, such as the Confusion Assessment Method-ICU (CAM-ICU) [21]. All four domains of the CAM-ICU, anchored on the presence of inattention, are evaluated in a focused patient assessment usually taking less than 2 min to complete. The CAM ICU scale is recognized as one of the leading assessment tools for delirium in the ICU. It has undergone extensive development, validation, and is routinely utilized [22,23].

Secondary endpoints

the full list of secondary endpoints is provided in **Box 2**.

Randomization and sequence generation

The randomisation will be performed using CleanWEB, a 24/7 online centralise procedure service running. 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

The number of experimental units per block will be kept confidential to avoid prediction of future patient's allocation. 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). Allocation concealment will be ensured, as CleanWeb services will not release the randomization code until the patient has been recruited into the trial. Patient allocation will only be disclosed after the enrolment and the dedicated statistician will be blinded to the arm's allocation until the end of analysis.

Follow-up

ICU stay

In both groups, patients will have a standardized management of analgesia, sedation, delirium, MV weaning and early mobilization according to current guidelines. This will ensure that the tested strategy is efficient by itself when applied along with other recommended clinical practices in ventilated patients, especially those known to have an impact on delirium occurrence. 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. Nurses in charge will have at their disposal a daily sheet including standard surveillance and clinical pathways to follow according to surveillance. Clinical pathways aim to plan, rationalize, and standardize multiprofessional management of patients with similar health problems based on recommendations to limit the variability of practices. Clinical pathways also ensure the traceability of these practices. Our clinical pathways were established according to currently available guidelines [6]. The daily sheets from D0 to D14 will be grouped in a booklet in A3 format to ensure better readability. An explicit training to use the booklet and the clinical pathways is planned before the start of the study (**see supplemental materials from 3 to 6**) and include:

1) Routine pain, agitation and delirium assessment will be performed every 12 hours (and more frequently as needed) using valid and reliable assessment tools, including the behavioural pain scale (BPS) [24], the Richmond Agitation Sedation Scale (RASS) [20] and the CAM-ICU [21], in accordance with guidelines [6,7].

2) Management of pain, agitation and delirium can be summarized as follows: Analgesia will be adapted to maintain BPS ≤ 4. Patients will be considered to be in significant pain if they have a BPS score of 6 or greater. Sedation will be adapted continuously to maintain a RASS score compatible with patient's management, i.e. from -1 to +1 (i.e., drowsy/alert to calm/restless) in general cases and from -5/-4 to -3 (i.e. deep sedation to moderate sedation) in case of severe acute respiratory distress syndrome (ARDS) or refractory intracranial hypertension. In case of RASS score ≥ -3 assess delirium every 12 hours using CAM-ICU and more often as needed. In case of significant pain (BPS ≥ 6), agitation (RASS ≥ +2) or delirium (CAM-ICU positive), the nurses will refer to specific clinical pathways including a physician alert process.

3) Clinical pathways to manage agitation will differ between groups since severe agitation with a RASS score ≥ +3 will require a temporary physical restraint (< 24 hours) in the restrictive use of PR group.

The PAD management strategies will be associated with other ICU interventions that are known to impact delirium occurrence or duration, i.e spontaneous awakening trial, spontaneous breathing trial and early mobilization protocols.

Follow-up consultation at D90

A consultation will be performed at D90 by a psychologist (or a trained investigator/study coordinator). This consultation will be carried out face-to-face or by teleconsultation. If the follow up is carried out by teleconsultation, an information note, specifying that no recording of the consultation will be made, will be sent to the patient. The non-objection of the patient will be sought and noted in the medical file. A core outcome set of measures will be assessed during the consultation, including cognitive capabilities, post-traumatic stress disorder, functional disability using appropriate scales (see Box 1 and figure 1).

STATISTICAL CONSIDERATIONS

Sample size calculation

In the literature, the number of delirium-free and coma-free days between D0 and D14 is estimated at 10.5 ± 3 days in the systematic PR group [25,26]. We therefore expect a 1-day reduction in delirium duration in the restrictive PR group with a number of delirium-free and coma-free days estimated at 11.5 days. We assumed a sample of 191 inclusions per arm to achieve 90% power to detect a difference of 1 day in the mean number of delirium-free and coma-free days over 14 days between the two groups at a 0.05 significance level. To allow the require power for the per-protocol analysis the sample size required is 422 (allowing for an estimated 9% loss to follow-up). Relying on the active participation of the 10 participating centres, we estimate that the inclusion time will be 38 months (assuming the number of inclusions at 1.1 patients per month per centre). To ensure the 422 planned inclusions and

the 3-month follow-up of all included patients, a research duration of 41 months is expected. Participant recruitment started on January 25th, 2021.

Statistical analyses

The number of delirium-free and coma-free days between D0 and D14 will be compared between the two experimental groups, systematic use group vs. restrictive use group by a Student's test or a Wilcoxon Rank-Sum test if no normality of criteria. If the patient dies within 14 days, the number of non-surviving days will be considered days of coma. If the patient is discharged before D14, after extubation, the number of days remaining will be considered delirium-free and coma-free days. If the patient is discharged before D14, always in MV, the number of days remaining will be considered delirium days. The main analysis will be in intent to treat (ITT), that is, patients will be analysed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analysed in the arm of management received. For the analysis of patients who leave the service before D14, we will perform a sensitivity analysis, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14, by a linear regression with adjustment on these 3 continuous factors. 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. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of invasive MV. In case if significant interaction, a sub-group analysis will be performed.

Secondary analyses will be performed in ITT and then in Per-protocol. The continuous secondary criteria of duration and cumulative doses of sedative agents', analgesics and or antipsychotics between D0 and D14 will be compared between the two experimental groups, systematic use group vs. restrictive use group, by a Student test or a Wilcoxon Rank-Sum test. The categorical secondary criteria will be compared by a Chi-square test or an exact Fisher test if appropriate.

The significant level of all statistical analyses will be a two-sided 5% and the confidence interval at 95%. We will not perform adjustments for multiple outcomes in our 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 [27].

All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 4.0 or later. All analyses will be conducted by a statistician according to a prespecified statistical analysis plan. A full statistical analysis plan has been written and is available in **supplemental material 7**. All analyses results will be reported according to the Consolidated Standards of Reporting Trials (STROBE) 2010 guidelines [28].

Data collection and management

Data collection will be done in electronic format using CleanWeb software. The software will fulfil the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

We will collect data on primary and secondary endpoints, as well as potential risk factors of delirium (ICU medication, comorbidities, and complications) detailed in **table 1**.

The data of this study will be available upon reasonable request from the corresponding author. The data will not be publicly available due to privacy or ethical restrictions.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in any of the phases of this study. Results of the trial will be made available to all participants via ClinicalTrials.gov as well as by email notification.

TRIAL STATUS

Recruiting. The first inclusion occurred on the 21st of January 2021 and the recruiting period will last 39 months. On March 12th 2024, 422 patients have been included and follow-up is ongoing.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this non-interventional human research study. AP-HP has obtained the favourable opinion of the independent ethics committee "Comité de Protection des Personnes (CPP) ILE DE FRANCE III – PARIS (CPP19.09.06.37521) for the study protocol (version R2D2−05.0; March 3, 2023). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol must be sent to the sponsor for approval. Once approval has been received from the sponsor, it must also obtain approval from the CPP before the amendment can be implemented. The information sheet and the consent form can be revised, if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research mentioned in 3° of this article (like R2D2 protocol) can be carried out on a person without his/her free and informed non opposition, obtained in oral after the person has been given the information specified in Article L.1122-1 of said Code.

The trustworthy persons/relatives of eligible patients will be informed of the modalities of implementation of the study through an information note and a consent form (see supplemental material 1) and oral explanations given by the investigating physician or any qualified person. This

information and consent forms will also be given to the patient concerned as soon as his neurological condition allows it.

Indeed, at the time of inclusion, the person participating in the research is often not in a state to give their consent; the inclusion in the R2D2 protocol is therefore done without prior agreement of the patient. Inclusion in the R2D2 protocol is done as soon as the patient is consecutively hospitalized in ICU and requires IMV: it is therefore not always possible to obtain the consent of the person before his inclusion in the trial.

The protocol therefore provides that the consent of this person is not systematically sought at inclusion and that only the non-opposition of family members or the trusted person is sought, and the informant (investigator or collaborator) will have sufficient time (the first 3 days of the patient's resuscitation) to proceed with clear and informed information, imperatively before the patient's inclusion in the research.

The information will be given to the patient and his consent will be sought at the time when his neurological state allows it.

The information and the collection of the consent of the patient or trusted person/relative is collected by the principal investigator, or by a physician who represents him/her, or by a qualified person in the participating centre.

Thus, 2 types of information document are provided for:

- one for the trusted person/close relative if he/she is present at the time of inclusion when the patient is unable to be informed.

- one for the patient as soon as he/she is able to consent to the continuation of the research.

A copy of the information document is given to the person participating in the research. The information given to the subject will be recorded in his or her medical file. Subjects may exit the study at any time and for any reason.

DATA COLLECTION AND QUALITY CONTROL

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information relating to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised. Under no circumstances should the names, addresses and other protector identifiers of the subjects involved be shown.

A data monitoring committee (DMC) has not been convened, on the grounds that the study is low risk. This has been approved by the Sponsor, Steering Committee, and the independent Ethical Board. The research data will be collected and monitored using an eCRF through CleanWEB Electronic Observation Book and will be centralised on a server hosted by the AP-HP Operations Department. This research is governed by the CNIL 'Reference Method for processing personal data for clinical studies' (MR-001, amended). AP-HP, the sponsor, has signed a declaration of compliance with this 'Reference Method'.

An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording, and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by independent individuals appointed by the sponsor. The aims of the audits are to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

SAFETY CONSIDERATIONS

The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests. The physical restraint will be prescribed in case of agitation (see guideline in supplemental materials).

TRIALS OVERSIGHT COMMITTEES

Two oversight committees have been established to oversee the conduct of this trial, the Steering Committee and Scientific Committee, the composition of each is listed at the end of this paper.

PUBLICATION PLAN

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and the publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the R2D2 investigators' in the final manuscript. Rules on publication will follow international recommendations.[29]

Author contributions RS and LB contributed to the conception and design of the research protocol, assisted by CC and VG. RS, CC, and LB wrote the first draft of the protocol and this manuscript. RC designed the statistical analysis plan. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interest statement Romain Sonneville received grants from the French Ministry of Health and from LFB. Other authors declare no competing interests.

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PARIS, grant number PHRC-N 2017. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

FIGURE LEGEND

Figure 1. Flow diagram.

Mechanical ventilation, RASS Richmond Agitation Sedation Scale, CAM-ICU Confusion Assessment Method for the ICU, MMSE Mini Mental State Evaluation, FAB Frontal Assessment Battery, IES-R Impact of Events Scale-revised, IPREA Inconforts des Patients de REAnimation, GOS-E Glasgow Outcome Scale-Extended, FIM Functional Independence Measure, MRC Medical Research Council Scale.

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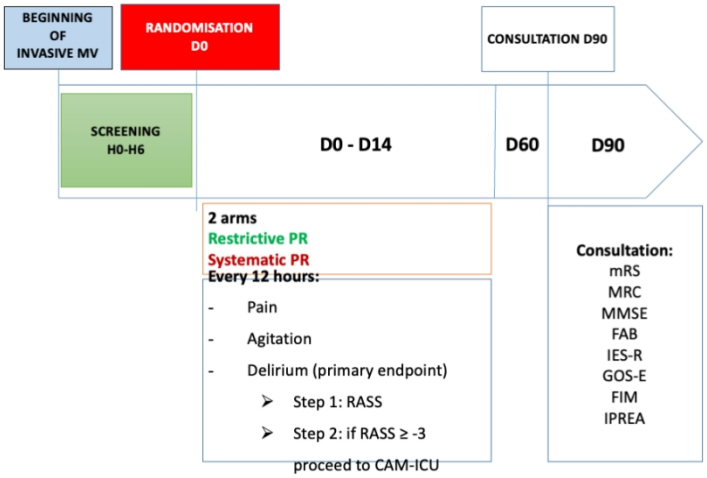

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Mechanical ventilation, RASS Richmond Agitation Sedation Scale, CAM-ICU Confusion Assessment Method for the ICU, MMSE Mini Mental State Evaluation, FAB Frontal Assessment Battery, IES-R Impact of Events Scale-revised, IPREA Inconforts des Patients de REAnimation, GOS-E Glasgow Outcome Scale-Extended, FIM Functional Independence Measure, MRC Medical Research Council Scale.

338x190mm (95 x 95 DPI)

Restrictive use of Restraints and Delirium Duration in ICU (R2D2-ICU): protocol for a multicenter parallel-group open label randomized controlled trial

SUPPLEMENTAL MATERIAL 1: SPIRIT CHECKLIST

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4 P20
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P20
Funding	4	Sources and types of financial, material, and other support	P24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 P23
	5b	Name and contact information for the trial sponsor	P1 P24
	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	P23
	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)	P23
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	P6

	6b	Explanation for choice of comparators	P6 P10
Objectives	7	Specific objectives or hypotheses	P7 BOX1
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)	P9 P15
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	P13
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)	P10 BOX2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10 TABLE1
	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)	P10 SM3-SM6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P21
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P23 TABLE1 SM3-SM6
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	P14 BOX1
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)	TABLE1 FIGURE1
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	P17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P13

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	P15
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	P15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P15 P21
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P15

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	P21
	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	P21
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	P21
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	P17 SM7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P17 SM7
	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)	P17 SM7

Methods: Monitoring

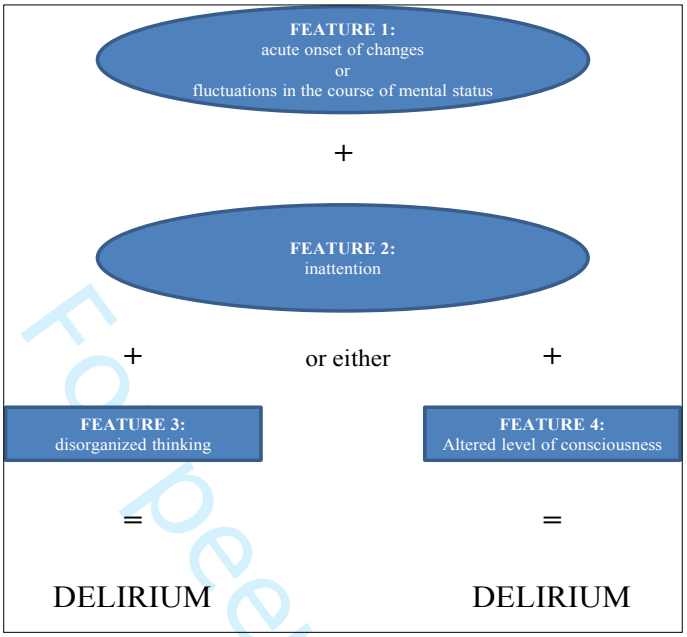
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NOT APPLICABLE
	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	NOT APPLICABLE
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	P21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NOT APPLICABLE
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P20
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)	P20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P9 TABLE1 P19 P20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NOT APPLICABLE
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	P20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P24
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	P20
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	NOT APPLICABLE

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	P20
	31b	Authorship eligibility guidelines and any intended use of professional writers	P20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NOT PROVIDE
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	NOT APPLICABLE

SUPPLEMENTAL MATERIAL 2: DELIRIUM ASSESSEMENT

CAM = Confusion Assessment Method

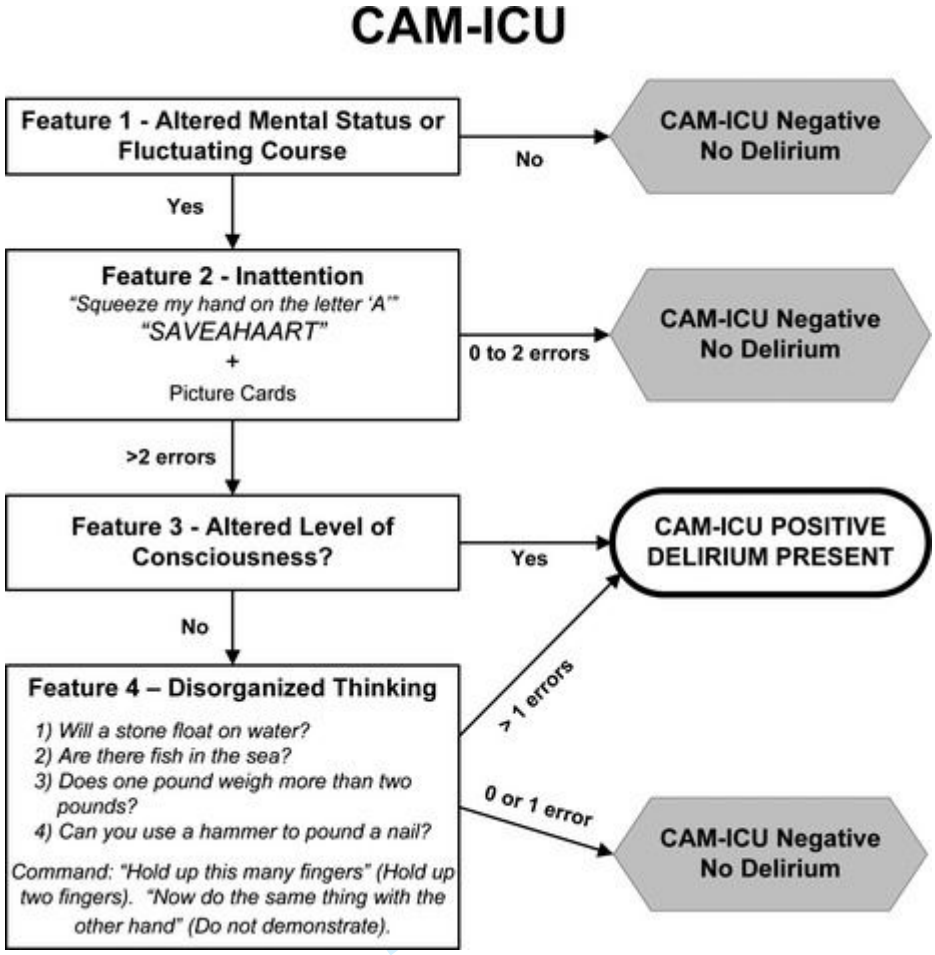
The Confusion Assessment Method (CAM) was created in 1990 by Dr. Sharon Inouye, and it was intended to be a bedside assessment tool usable by non-psychiatrists to assess for delirium [38]. Delirium is defined in terms of four diagnostic features, and is deemed positive when Feature 1 and Feature 2 and either Feature 3 or 4 are present (see CAM and CAM-ICU schematics).



CAM Confusion Assessement Method	The diagnosis of delirium by CAM requires the presence of **BOTH** features ***A*** and ***B***	
	A = acute onset and fluctuating course	Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: ➢ come and go? ➢ fluctuate during the day? ➢ increase/decrease in severity?
	B = Inattention	Does the patient: ➢ have difficulty focusing attention? ➢ become easily distracted? ➢ have difficulty keeping track of what is said?
	AND the presence of **EITHER** feature **C** or **D**	
	C = Disorganized thinking	Is the patient's thinking ➢ disorganized ➢ incoherent For example does the patient have ➢ rambling speech/irrelevant conversation? ➢ unpredictable switching of subjects? ➢ unclear or illogical flow of ideas?
	D = Altered level of consciousness	Overall, what is the patient's level of consciousness: ➢ alert (normal) ➢ vigilant (hyper-alert) ➢ lethargic (drowsy but easily roused) ➢ stuporous (difficult to rouse) ➢ comatose (unrousable)

The Confusion Assesement Method for the Intensive Care Unit (CAM-ICU)

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course A. Is there evidence of an acute change in mental status from baseline? **B.** Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidence by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Coam Glasgow Scale?	☐	☐
II. Inattention Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answerson either the visual or auditory components of the Attention Screening Examination (ASE)	☐	☐
III. Disorganized thinking Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stonefloat on water 2. Are there fish in the sea 3. Does 1 pound weigh more that 2 pounds 4. Can you use a hammer to pound a nail Commands 1. Are you having unclear thinking? 2. Hold up this many fingers(examiner holds 2 fingers in front of the patient) 3. Now do the same thing with the other hand (withoutholding the 2 fingers in front of the patient) (If the patient is already extubated from the ventilator, determine wether the patient's thinking is disorganized or incoherent, sucha s rambling or irrelevant conversation, unclear or illogical flow or ideas, or unpredictable switching from subject to subject)	☐	☐
IV. Altered level of consciousness Is the patients's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environement and interacts appropriately Vigilant: hyperalert Lethargic drowsy but easily aroused, unaware of some elements in the environement or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unware of some or all elements, in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapes back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding	☐	☐
Overall CAM-ICU Assessment (Features I and II and either feature III or IV): YES ☐ NO ☐		



The CAM-ICU is an adaptation of the CAM tool for use in ICU patients (e.g., critically ill patients on or off the ventilator) using nonverbal, objective tests derived through a comprehensive literature review and consulation with numerous delirium experts. (1). The CAM-ICU underwent extensive validation in the ICU setting and is, therefore, one of the delirium scores recommended by international guidelines (2). The Richmond Agitation Sedation Scale (RASS) is a component of the CAM-ICU (Feature 4: Altered Level of Consciousness).

Références

1. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941-8).
2. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001 Dec 5;286(21):2703–10.

SUPPLEMENTAL MATERIAL 3: DAILY CRITICAL CARE MANAGEMENT OF SYSTEMATIC PHYSICAL RESTRAINT

GROUP
SYSTEMATIC PHYSICAL RESTRAINT

DATE
From D0 to D14 __ __/__ __/____

SCHEDULE (X = mandatory; x = if needed)	AM					PM											AM						
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
PAIN/SEDATION-AGITATION/DELIRIUM ASSESSEMENTS																								
I : Assess pain using BPS: TARGET ≤ 4 Refer to the specific clinical pathway on the back of the sheet if BPS > 4.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
II : Assess agitation/sedation using RASS : TARGET -1/0/+1 (-4/-5 in case of ARDS or ICH) Refer to the specific clinical pathway on the back of the sheet if RASS ≥ +3. **Mention physical restraint session |----|**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
III : Assess delirium only if RASS ≥ - 3 using CAM-ICU **Refer to the specific clinical pathway on the back of the sheet** criteria I +II and criteria III and /or IV present - Criteria I present (Yes/No) - Criteria II present (Yes/No) - Criteria III present (Yes/No) - Criteria IVpresent (Yes/No)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY SCREEN																								
I : SAT safety screen Follow and complete the clinical pathway on the back sheet. If appropriate do SAT and go to SBT. Mention both sedatives STOPS (SAT) and RESTARTS (R) times.	ONCE A DAY BETWEEN 8AM AND NOON																							
II : SBT safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do SBT. Mention both SBT, EXTUBATION (E), and REINTUBATION (R).	ONCE A DAY BETWEEN 8AM AND NOON																							
III : EM safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do EM according to patients'status Mention both (MAP, MAA, PV, BL, MFP, MFA, walk)	ONCE A DAY BETWEEN 8AM AND NOON																							

BPS = Behavioral pain scale; RASS = Richmond Agitation-Sedation Scale; SAT= spontaneous awakening trial; SBT = spontaneous breathing trial; EM = early mobilization

SUPPLEMENTAL MATERIAL 4: CLINICAL PATHWAYS ACCORDING TO BPS, RASS AND CAM-ICU ASSESSMENTS FOR THE SYSTEMATIC PHYSICAL RESTRAINT GROUP

Clinical pathways according to BPS, RASS, and CAM-ICU assessments

SIGNIFICANT PAIN: BPS ≥ 6

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of pain**

Check for a serious painful event (myocardial infarction, thromboembolic event, ileus, peritonitis)

2) **Choose the appropriate analgesic**

a. Use the WHO analgesic scale to treat a nociceptive pain.
   First WHO level: acetaminophen and/or nefopam
   Second WHO level: dextropropoxyfen or tramadol or nalbuphin.
   Third WHO level: morphine or fentanyl or patient-controlled analgesia.

b. Use a spasmolytic intestinal drug to treat an intestinal spasm.

c. Use centrally acting muscle relaxants to treat a muscle contracture.

d. d. Use anti-inflammatory nonsteroid drugs (AINS) to treat an inflammatory pain if first and second WHO level analgesics are inefficient.

SIGNIFICANT AGITATION: RASS ≥ +2

REFER TO THE PHYSICIAN IN CHARGE

1) **Physical restraint if RASS ≥ +3**
2) **Diagnose the source of agitation***
3) **Choose the appropriate drug**

a. Is the patient in pain? Cf. supra

b. Is the patient talking about anxiety? Consider use of benzodiazepine.

c. Is the patient delirious? Cf. infra.

d. Consider withdrawal syndrome if patient is a psychoactive and/or a third WHO level drug user or received continuous sedation in the last 48 hrs: test reintroduction of the drug, consider clonidine to withdraw previous treatment

REASSESSEMENT WITHIN 4 HOURS

DELIRIUM = CAM-ICI POSITIF

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of delirium***
2) **Choose the appropriate drug**

a. Use a neuroleptic in case of agitation (RASS ≥ +2)
   -Haldol® if the patient is confused or describing hallucinations
   -Nozinan® in case of predominant anxiety or sutained RASS ≥ 3

b. Use dexmedetomidine idf neuroleptics are inefficient or proscribed

REASSESSEMENT WITHIN 6 HOURS

*Serious painful event, brain injury, fever or sepsis), hydroelectrolytic disorders, acute urinary retention, fecal impaction, analgesic-associated

SUPPLEMENTAL MATERIAL 5: DAILY CRITICAL CARE MANAGEMENT OF SYSTEMATIC PHYSICAL RESTRAINT

GROUP
RESTRICTIVE PHYSICAL RESTRAINT

DATE
From D0 to D14 __ __/__ __/____

SCHEDULE (X = mandatory; x = if needed)	AM					PM												AM						
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
PAIN/SEDATION-AGITATION/DELIRIUM ASSESSEMENTS																								
I : Assess pain using BPS: TARGET ≤ 4 Refer to the specific clinical pathway on the back of the sheet if BPS > 4.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
II : Assess agitation/sedation using RASS : TARGET -1/0/+1 (-4/-5 in case of ARDS or ICH) Refer to the specific clinical pathway on the back of the sheet if RASS ≥ +3. **Mention physical restraint session |----|**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
III : Assess delirium only if RASS ≥ - 3 using CAM-ICU **Refer to the specific clinical pathway on the back of the sheet** criteria I +II and criteria III and /or IV present - Criteria I present (Yes/No) - Criteria II present (Yes/No) - Criteria III present (Yes/No) - Criteria IVpresent (Yes/No)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY SCREEN																								
I : SAT safety screen Follow and complete the clinical pathway on the back sheet. If appropriate do SAT and go to SBT. Mention both sedatives STOPS (SAT) and RESTARTS (R) times.	ONCE A DAY BETWEEN 8AM AND NOON																							
II : SBT safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do SBT. Mention both SBT, EXTUBATION (E), and REINTUBATION (R).	ONCE A DAY BETWEEN 8AM AND NOON																							
III : EM safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do EM according to patients'status Mention both (MAP, MAA, PV, BL, MFP, MFA, walk)	ONCE A DAY BETWEEN 8AM AND NOON																							

BPS = Behavioral pain scale; RASS = Richmond Agitation-Sedation Scale; SAT= spontaneous awakening trial; SBT = spontaneous breathing trial; EM = early mobilization

SUPPLEMENTAL MATERIAL 6: CLINICAL PATHWAYS ACCORDING TO BPS, RASS AND CAM-ICU ASSESSMENTS FOR THE RESTRICTIVE PHYSICAL RESTRAINT GROUP

Clinical pathways according to BPS, RASS, and CAM-ICU assessments

SIGNIFICANT PAIN: BPS ≥ 6

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of pain**

Check for a serious painful event (myocardial infarction, thromboembolic event, ileus, peritonitis)

2) **Choose the appropriate analgesic**

a. Use the WHO analgesic scale to treat a nociceptive pain.
   First WHO level: acetaminophen and/or nefopam
   Second WHO level: dextropropoxyfen or tramadol or nalbuphin.
   Third WHO level: morphine or fentanyl or patient-controlled analgesia.
b. Use a spasmolytic intestinal drug to treat an intestinal spasm.
c. Use centrally acting muscle relaxants to treat a muscle contracture.
d. d. Use anti-inflammatory nonsteroid drugs (AINS) to treat an inflammatory pain if first and second WHO level analgesics are inefficient.

SIGNIFICANT AGITATION: RASS ≥ +2

REFER TO THE PHYSICIAN IN CHARGE

1) **Physical restraint if RASS ≥ +3**
2) **Diagnose the source of agitation***
3) **Choose the appropriate drug**

a. Is the patient in pain? Cf. supra
b. Is the patient talking about anxiety? Consider use of benzodiazepine.
c. Is the patient delirious? Cf. infra.
d. Consider withdrawal syndrome if patient is a psychoactive and/or a third WHO level drug user or received continuous sedation in the last 48 hrs: test reintroduction of the drug, consider clonidine to withdraw previous treatment

REASSESSEMENT WITHIN 4 HOURS

DELIRIUM = CAM-ICI POSITIF

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of delirium***
2) **Choose the appropriate drug**

a. Use a neuroleptic in case of agitation (RASS ≥ +2)
   -Haldol® if the patient is confused or describing hallucinations
   -Nozinan® in case of predominant anxiety or sutained RASS ≥ 3
b. Use dexmedetomidine idf neuroleptics are inefficient or proscribed

REASSESSEMENT WITHIN 6 HOURS

*Serious painful event, brain injury, fever or sepsis), hydroelectrolytic disorders, acute urinary retention, fecal impaction, analgesic-associated

SUPPLEMENTAL MATERIAL 7: STATISTICAL ANALYSIS PLAN FOR A MULTICENTER PARALLEL-GROUP OPEN LABEL RANDOMIZED CONTROLLED TRIAL

(VERSION DECEMBER 12 2023)

Table

1 ENDPOINTS

Endpoints will be compared between randomization groups (restrictive use of PR vs. systematic use of PR).

1.1. Primary endpoint

It will be the number of delirium-free or coma-free days, defined as the number of days in the first 14 days after randomization during which the patient was alive without delirium or not in coma from any cause. This endpoint will be assessed twice a day by the French validated translation of the Richmond Agitation Sedation Score (RASS) and CAM-ICU by well-trained nurses. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score > or = -3 will be assessed for delirium with the use of the CAM-ICU scale.

1.2. Secondary endpoints

1.1.1 Delirium duration until ICU discharge

This criterion is defined by the number of days on delirium until ICU discharge, the proportion of positive CAM-ICU until ICU discharge.

1.1.2 Incidence of delirium between D0 and D14

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 and D14.

1.1.3 Incidence of delirium until ICU discharge

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 until ICU discharge.

1.1.4 Agitation duration between D0 and D14

This criterion is defined by the number of days alive with agitation (RASS ≥ 2) between D0-D14.

1.1.5 Exposure to analgesic (opioids) between D0 and D14

This criterion is defined by the total cumulative dose of opiod analgesics (and subclass of opioids) between D0 and D14.

1.1.6 Exposure to propofol between D0 and D14

This criterion is defined by the total cumulative dose of propofol between D0 and D14.

1.1.7 Exposure to benzodiazepines between D0 and D14

This criterion is defined by the total cumulative dose of benzodiazepines as anxiolytic between D0 and D14.

1.1.8 Exposure to antipsychotic agents between D0 and D14

This criterion is defined by the total cumulative dose of antipsychotics agents (Haloperidol, Levomepromazine and Cyamemazine) between D0 and D14.

1.1.9 Exposure to dexmetomidine between D0 and D14

This criterion is defined by the total cumulative dose of dexemtomidine between D0 and D14

1.1.10 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

This criterion is defined by the total number of hours without mechanical ventilation between D0 and D14.

1.1.11 Patient mobility according to the visual global mobilisation score between D0 and D14

This criterion is defined by the Median of Mobilisation capacity and rate of patients > 2 on a visual scale ranging from 0 (no mobilisation) to 4 (ambulation) between D0- D14.

1.1.12 Incidence of self-extubation and device removal between D0 and D14

This criterion is defined by the rate of patients with at least one self-extubation or any device removal (Central catheter, arterial catheter or urinary catheter) between D0 and D14.

1.2.13 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

This criterion is defined by the rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel between D0-D14 (at least one ulcer of grade III or IV per patient).

1.2.14 ICU and hospital lengths of stay

This criterion is defined by the number of hospitalization day.

1.2.15 In-ICU and in-hospital mortality

This criterion is defined by the mortality rate on ICU stay and during hospitalization.

1.1.16 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

This criterion is defined by:

- The rate of patients with at D90 an altered cognitive capability defined as a MMSE (Mini Mental State Examination) ≤ 24 points
- The rate of patients with a frontal syndrome defined as a FAB (Frontal Assessment Battery at Bedside) < 15 points
- The rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder (PTSD) defined as a R-IES (Revised-Impact of events scale) ≥ 33 points
- The rate of patients with a functional disability defined as a GOS-E (Glasgow Outcome Scale – Extended) ≤ 6 points
- The rate of patients with functional independence, evaluated by the FIM (Functional Independence Measurement)

2 GENERAL CONSIDERATIONS

2.1. Flowchart

A flowchart following *Consolidated Standards of Reporting Trials (CONSORT)* standards, describing patients flow throughout the study, included and randomized, will be provided. The flowchart will specify the number of patients in each arm and describe loss of patients during the study.

2.2. Level of statistical significance

In this study, the statistical level of significance (Type I error) will be fixed at 5%.

2.3. First day of patient- follow-up (D0)

The first day of patient follow-up (D0) is the day of randomization. This day is the reference day which will be used as the initial date in the calculation of all delays.

3 STATISTICAL ANALYSIS

3.1. Descriptive analysis

The variables that will be described are as follows:

- Comorbidities/Demographic data of the included population and at ICU admission

- Treatments administred at ICU admission (Ketamine, Etomidate, Propofol and others)
- Clinical and biological data at ICU admission and from D1 to D14
- Clinical scores at ICU admission and from D1 to D14
- End-of-study data/Discharge assessment
- Clinical scores at D90

The dedicated score to assess the delirium-free and coma-free days will be described per day – morning and evening assessment. A time plot will be provided to allow a graphical description of the quality assessment between D0 and D14. Melatonin exposure will be described per day and on total, with normalization on number of days on ICU to allow patients discharged before D14 to be taken into account.

All qualitative variables will be described by their number and corresponding frequency. Quantitative variables will be described by their min and max, mean and standard deviation, median, Q1 and Q3. For each variable, the number and frequency of missing data will be reported. The description will be made for all patients and then according to the randomisation group (systematic PR vs. restrictive PR). The total number of patients and in each group will be specified. Melatonin exposure description will be also made according to the use of different devices in the medical room (i.e. earplugs, masks, natural light).

Results of descriptive analysis will be presented in tables as follows:

	Total population (N=)	Systematic PR (N=)	Restrictive PR (N=)
Quantitative variable			
	Range	Range	Range
	Median [IQR]	Median [IQR]	Median [IQR]
	Mean (SD)	Mean (SD)	Mean (SD)
	NA (n (%))	NA (n (%))	NA (n (%))
Qualitative variable			
« First modality »	% (n/N)	% (n/N)	% (n/N)
« Second modality »	% (n/N)	% (n/N)	% (n/N)
Missing	% (n/N)	% (n/N)	% (n/N)

3.2. Analysis of the primary endpoint

Analysis set

The main analysis will be in intent to treat (ITT), that is, patients will be analyzed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analyzed in the arm of management actually received.

Descriptive statistics and graphical representation

Results of CAM-ICU (Positive/Negative/Not done) will be described each day and for each evaluation, with sample size and proportion of patients in each modality, from D0 to D14, on total population and according to the randomisation group.

We will construct a variable summarizing CAM-ICU results each day (Morning CAM-ICU positive and evening CAM-ICU negative/Morning CAM-ICU negative and evening CAM-ICU positive/Both morning and evening CAM-ICU positives/Both morning and evening CAM-ICU negatives) from D0 to D14. This variable will be described with sample size and proportion of patient in each modality, from D0 to D14, on total population and according to the randomisation group.

The number of patients without coma and delirium will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The number of delirium-free and coma-free days will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made for all patients and then according to the randomisation group.

Statistical methodology

A variable corresponding to the number of delirium-free and coma-free days between D0 and D14 (primary endpoint) will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where all CAM-ICU evaluations (morning, evening or supplementary CAM-ICU evaluations) are negative. Each day, from D0 to D14, primary endpoint for ICU discharged patients will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days will be considered days of coma.

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all RASS or CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by days with coma.
- If there are non-missing data before and after the missing data and data before missing data show RASS ≥ -3 (patient not considered comatose), missing result will be imputed by days without coma.
- It will be considered that a delirium day cannot be a coma day and vice versa, meaning that in case of days with RASS ≤ -4 (patient considered comatose), and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value and in case of days with positive CAM-ICU and missing RASS, RASS results are imputed by no coma days.
- In case of missing data until D14, a last value carried forward imputation method will be performed, for both RASS and CAM-ICU

The number of coma or delirium free days between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon text as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3. Analyses of secondary endpoints

3.2.1 Delirium duration until ICU discharge

Analysis set

This analysis will be performed on the sub-population of patients having at least one day of delirium between D0 and D14.

Descriptive statistics and graphical representation

The number of days with delirium (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The proportion of positive CAM-ICU until ICU discharge will be described using frequencies, on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The number of CAM-ICU performed until ICU discharge will be constructed for each patient. This variable will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

Statistical methodology

The number of days with delirium will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where at least one of the morning, evening or supplementary CAM-ICU evaluations is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.

- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value
- In case of missing data until D14, a last value carried forward imputation method will be performed

Number of days with delirium between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

The proportion of positive CAM-ICU until ICU discharge will be compared between randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test. Proportions of positive CAM-ICU will be presented with 95% confidence intervals according to the randomisation group.

The number of CAM-ICU performed until ICU discharge will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.2 Incidence of delirium between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with delirium (constructed variable, see below) will be described each day, between D0 and D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

Patients with delirium between D0 and D14 are defined as patients experiencing delirium at least one day from D0 to D14, a delirium day being a day with at least one of the morning, evening or supplementary CAM-ICU evaluations that is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value.
- In case of missing data until D14, a last value carried forward imputation method will be performed

Rate of patients with delirium between D0 and D14 will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients with delirium between D0 and D14 with 95% confidence intervals and according to the randomisation group.

3.2.3 Agitation duration between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The number of days with agitation (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

The number of days with agitation between D0 and D14 will be a constructed variable, indicating for each patient the total amount of days where the patient is alive with RASS ≥ 2. Imputation methods for this endpoint are as follows:

- If the patient is discharged before D14, after extubation, the remaining days are considered no agitation days.
- If the patient is discharged before D14, always in MV, the remaining days are considered agitation days.
- If the patient dies within 14 days, the number of non-surviving days are considered as no agitation days.

In case of partial missing RASS evaluation (i.e. at least one of the morning, evening or supplemental RASS evaluation is not missing), we will impute the missing RASS evaluation by the non-missing evaluation of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with days with total missing RASS evaluation, we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by coma days (i.e. RASS ≤ -4).
- In case of missing data until D14 for RASS score, a last value carried forward imputation method will be performed

The number of days with agitation between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.2.4 Exposure to analgesic (opioids) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Doses of analgesic (opioids) will be described each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Total cumulative dose of analgesic (opioids) from D0 to D14 will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. Total cumulative doses of analgesic (opioids) between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.5 Exposure to propofol between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative doses of propofol from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of propofol between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.6 Exposure to benzodiazepines between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative dose of benzodiazepines from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of benzodiazepines between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.7 Exposure to antipsychotic agents between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose from D0 to D14 for each antipsychotic agent (i.e. Haloperidol, Levomepromazine and Cyamemazine) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The same description will be made for total cumulative dose of all antipsychotic agent.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of antipsychotic agents between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.8 Exposure to dexmedetomidine between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose of dexmedetomidine will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical method

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of dexmedetomidine between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.9 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The number of patients exposed to IMV will be described each day, from D0 to D14, using frequencies. The description will be made for the total population and according to the randomisation group. The same description will be made for the number of patients exposed to IMV between D0 and D14.

The total amount of hours under IMV between D0 and D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For invasive mechanical ventilation exposure, it will be considered that:

- If the patient is discharged before D14, after extubation, the remaining days are not considered as days with exposure to invasive mechanical ventilation
- If the patient is discharged before D14, always in MV, the remaining days are considered as days with MV
- If the patient is discharged before D14, not in MV, the remaining days are considered as days without MV
- If the patient dies within 14 days, the remaining days are considered as days with MV

Exposure to IMV will be compared according to the randomisation group using student's t-test or Wilcoxon as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.10 Patient mobility according to the visual global mobilisation score between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The visual global mobilisation score will be descripted each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The visual global mobilisation score will be also descripted for the total D0-D14 period, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The rate of patients with global mobilisation score > 2 will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

Boxplots of the visual global mobilisation score from D0 to D14 will be realized to allow graphical representation of patient mobility.

Statistical methodology

There will be no methods for replacing missing data. The median of the visual mobilisation score on the D0-D14 period will be firstly normalized by the number of days under ICU hospitalization, to allow discharge from ICU or death before D14 to be taken into account. Normalized visual mobilisation score on the D0-D14 period will be compared between randomisation group using Wilcoxon test. Results will be presented using median and p-value of the test.

3.2.11 Incidence of self-extubation and device removal between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patient experiencing self-extubation will be described for each device (self-extubation, removal of central catheter, arterial catheter or urinary catheter), each day for D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The same description will be realized for self-extubation or any device removal and for any device removal only.

Statistical methodology

The proportion of patients with self-extubation or any device removal will be compared between randomisation groups using chi-squared or Fisher test as appropriate. The same comparison between randomisation groups will be made for patients experiencing self-extubation only and for patients experiencing any device removal only. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.2.12 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patients with skin lesions will be described for each skin lesion (wrist, heel, sacrum, other), each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

The proportion of patients with at least one of the four types of skin lesions (wrist, heel, sacrum, other) will be described, each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

Statistical methodology

The proportion of patients with wrist lesions, the proportion of patients with heel lesions, the proportion of patients with sacrum lesions, and the proportion of patients with other skin lesions between D0 and D14 and according to the randomisation group will be analysed individually using chi-squared or Fisher test as appropriate. Results will be presented using p-value of the tests as well as proportion of patients with each lesion with their 95% interval confidence and according to the randomisation group.

The same analysis will be realized for patients having at least one of the four types of skin lesion (wrist, heel, sacrum, other) between D0 and D14 using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.2.13 ICU and hospital lengths of stay

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The ICU length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The hospital length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For patients dying within 14 days, it will be considered that they stayed in ICU and hospital from ICU admission to date of death and from hospital admission to date of death respectively. In case of missing date for ICU discharge or hospital discharge outside patients who died within 14 days, the date of discharge from ICU/hospital will be imputed by the date of the patient's last news.

ICU length of stay and hospital length of stay will be analysed between according to randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.2.14 In-ICU and in-hospital mortality

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The proportion of dead patients will be described each day, from D0 to D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

To allow lost-to-follow up patients to be taken into account, a Kaplan-Meier model will be realized, the event of interest being in-ICU death or in-hospital death. We will perform a log rank

test to compare survival distributions according to the randomisation group. Results will be presented using p value of the log rank test, as well as proportion of death at day 90 between randomisation groups with their 95% interval confidence and according to the randomisation group.

3.2.15 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with altered cognitive capabilities at D90, the rate of patients with a frontal syndrome at D90, the rate of patients with a possible diagnosis of PTSD, the rate of patients with a functional disability at D90 and the rate of patients with a functional independence at D90 will be described using frequencies. These descriptions will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no imputation for missing data. Each individual endpoint will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test as well as proportion of patients with altered cognitive capabilities at D90, proportion of patients with a frontal syndrome at D90, proportion of patients with a possible diagnosis of PTSD, proportion of patients with a functional at D90 and proportion of patients with a functional independence at D90. Each proportion will be provided with their 95% interval confidence and according to the randomisation group.

3.2.16 Center effect, age group effect and presence of coma at beginning of IMV effect

The center effect will be assessed by testing interaction between trial arm and the center in a linear regression modelling the number of delirium-free and coma-free days between D0 and D14. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of IMV. Results will be presented using coefficients of the linear regression with 95% confidence intervals as well as p-value of the tests. In case if significant interaction, a sub-group analysis will be performed.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2.

3.4. Sensitivity analysis

3.3.1 Number of days lived without coma and without delirium for patients leaving ICU before D14

This analysis will consist of a multivariate linear regression predicting the number of days lived without coma and without delirium in the sub-population of patients leaving ICU before D14, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2. Missing values for MV exposure will be imputed using same methodologies as described in §3.2.9. There will be no imputation for sedation time.

3.3.2 Physical restraint exposure

A sensitivity analysis will be performed on primary endpoint for patients whose exposure to either restrictive or systematic RA has been fully respected over the 14 days according to the predefined rules. In addition, an analysis will be carried out on patients who have had no change in their exposure to RA during the 14 days or until discharge from intensive care after extubation. Sedative exposure at intubation at D0

Sensitivity analysis for the primary endpoint will be performed on the sub-population of patients exposed to sedative agents at intubation at D0.

3.5. Subgroup analysis

3.4.1 Center effect, age group effect and presence of coma at beginning of IMV effect

In case of significant interaction for analyses described in §3.2.16, a sub-group analysis will be performed for the prediction of number of delirium-free and coma-free days between D0 and D14. An ANOVA will be used for comparison of number of delirium-free and coma-free days from D0 to D14 between centres. We will use Student's t-test test or Wilcoxon test as appropriate to compare number of delirium-free and coma-free days from D0 to D14 between age groups and according to presence of coma at beginning of IMV. Results will be presented using mean or median as appropriate and p-values of the test.

3.4.2 Covid patients

A subgroup analysis will be performed on patients exposed to COVID for the comparison of number of delirium-free and coma-free days between D0 and D14 and according to COVID exposure. We will use Sudent's t-test or Fisher test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

4 SOFTWARE

Statistical analyses will be made using R v. 4.2.1 or later (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/), or SAS Version 9.4 or later (SAS Institute Inc., Cary,NC).1/1/0001 12:00:00 AM

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Utilisation restrictive de la contention physique et durée du délirium en réanimation : un essai contrôlé randomisé. R2D2-ICU

Cette recherche est promue par l'Assistance Publique- Hôpitaux de Paris
Représentée par la Directrice de la
Délégation à la Recherche Clinique et à l'Innovation
1 avenue Claude Vellefaux
75010 Paris

NOTE D'INFORMATION - PATIENT N°1

Madame, Monsieur,

Le Docteur/ Le Professeur…… (nom, prénom), exerçant à l'hôpital ……, vous propose de participer à une recherche concernant votre état de santé.
Il est important de lire attentivement cette note avant de prendre votre décision ; n'hésitez pas à lui demander des explications. Si vous décidez de participer à cette recherche, un consentement écrit vous sera demandé.

1) Quel est le but de cette recherche ?

Les patients admis en réanimation peuvent souffrir d'agitation, ce qui est associé à une augmentation de la durée de ventilation mécanique et de séjour en réanimation. En effet, cette agitation peut conduire à l'arrachement des dispositifs médicaux comme les sondes urinaires et les perfusions … Afin de prévenir ces auto-arrachements, le personnel médical peut avoir recours à la contention physique.
La contention physique est définie comme l'utilisation des procédés qui empêchent ou limitent les capacités de mouvement volontaire pour protéger une personne d'un comportement estimé dangereux ou mal adapté.
Il n'existe aucune recommandation quant à la contention physique des patients admis en réanimation et bien que fréquemment utilisée, le bénéfice de la contention physique n'est pas clairement établi et pourrait même être délétère, c'est-à-dire nocif, dans ce contexte. Il n'existe, en effet, aucune relation démontrée entre le nombre d'auto-arrachements des dispositifs médicaux et le nombre de contentions physiques. Il existe cependant une relation complexe entre l'agitation, la dysfonction cérébrale aiguë (que les anglo-saxons appellent delirium) et la contention physique. Alors que la contention physique est mise en place pour éviter les risques potentiels liés à l'agitation, elle semble favoriser le délirium.

Le délirium, ou syndrome confusionnel aigu, est un terme générique pour définir un changement rapide de l'état mental (de quelques minutes à quelques jours) qui associe des troubles qui fluctuent au cours de la journée : une altération de la conscience avec une diminution de la capacité à fixer son attention, une modification du fonctionnement cognitif (désorganisation de la pensée, trouble de la mémoire…) et/ou une perturbation des perceptions non expliquée par des troubles mentaux préexistants. L'expression du délirium peut se manifester par de l'agitation.

Le délirium est un problème fréquent chez les patients admis en réanimation et la contention physique étant reconnue comme un facteur majeur de sa survenue, cette recherche porte donc sur l'effet de la contention physique sur la durée du délirium chez les patients hospitalisés en réanimation et sous ventilation mécanique. Pour répondre à la question posée dans la recherche, il est prévu d'inclure 422 patients dans quelques services de réanimation des établissements de soins participants situés en France.

2) En quoi consiste la recherche ?

Dans la recherche proposée, nous allons comparer, chez des patients ayant une prescription de contention physique comme vous, la durée du délirium chez des patients pour lesquels la contention physique est utilisée de manière systématique et chez des patients pour lesquels son utilisation sera limitée à des périodes d'agitation extrême. Après accord de votre part et signature du formulaire de consentement, l'une des deux stratégies vous sera attribuée par tirage au sort. Vous serez soit dans le groupe

pour lequel la contention physique sera appliquée de manière systématique, soit dans le groupe pour lequel la contention physique ne sera appliquée qu'en cas de période de forte agitation.

3) Quel est le calendrier de la recherche

La durée prévisionnelle de la recherche est de 41 mois et votre participation sera de 3 mois. Après la signature de votre consentement, lors de la première visite, le déroulement de la recherche sera le suivant : vous serez suivi(e) quotidiennement pendant 14 jours selon les pratiques de soin habituelles pour votre pathologie ou jusqu'à votre sortie de réanimation si vous sortez avant J14.
Une visite avec un psychologue sera réalisée 90 jours après votre inclusion dans l'étude. Lors de cette visite, vous devrez répondre à différents questionnaires ayant pour but d'évaluer votre force musculaire, vos capacités cognitives (mémoire, réflexion…), votre état psychologique, votre qualité de vie ainsi que votre parcours de soin (visite chez le médecin, hospitalisation…) depuis votre sortie de réanimation. Si vous ne pouvez pas venir pour cette consultation, vous serez joint par téléphone afin de recueillir les informations concernant votre qualité de vie depuis votre sortie de réanimation.

4) Quels sont les bénéfices liés à votre participation

En participant à cette recherche, vous bénéficiez d'un suivi médical étroit et spécifique pour lequel aucun frais supplémentaire ne vous sera demandé. Vous aurez une chance sur deux d'éviter la contention physique systématique qui est appliquée dans le traitement courant des patients atteints de votre pathologie.
Par ailleurs, vous contribuerez à une meilleure connaissance du recours à la contention physique chez les patients admis en réanimation et sous ventilation mécanique sur la durée du délirium.

5) Quels sont les risques et les contraintes prévisibles ajoutés par la recherche?

Aucun acte spécifique ne sera ajouté par la recherche comparativement aux soins habituels, il n'y a pas de risque supplémentaire par rapport à votre prise en charge habituelle.

Si vous acceptez de participer, vous devrez respecter les points suivants :

- Ne pas prendre part à un autre projet de recherche sans l'accord de votre médecin, ceci pour vous protéger de tout accident possible pouvant résulter par exemple d'incompatibilités possibles entre les thérapeutiques étudiées ou d'autres dangers
- Venir au rendez-vous. En cas d'impossibilité, nous vous remercions de contacter votre médecin le plus rapidement possible.
- Répondre aux questionnaires posés dans le cadre de la recherche, soit en face à face, soit par téléphone.
- Etre affilié(e) à un régime de sécurité sociale ou être bénéficiaire d'un tel régime.

6) Quelles sont les modalités de prise en charge médicale à la fin de votre participation ?

Votre prise en charge médicale à la fin de votre participation sera strictement la même que dans le cadre de votre prise en charge habituelle. Votre médecin pourra décider à tout moment de l'arrêt de votre participation, il vous en expliquera les raisons.

7) Si vous participez, comment vont être traitées les données recueillies pour la recherche ?

Dans le cadre de la recherche à laquelle l'AP-HP vous propose de participer, un traitement de vos données personnelles va être mis en œuvre pour permettre d'en analyser les résultats.

Ce traitement est nécessaire à la réalisation de la recherche qui répond à la mission d'intérêt public dont est investie l'AP-HP en tant qu'établissement public de santé hospitalo-universitaire.
A cette fin, les données médicales vous concernant et les données relatives à vos habitudes de vie seront transmises au Promoteur ou aux personnes ou partenaires agissant pour son compte, en France. Ces données seront identifiées par un numéro d'enregistrement. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Les données médicales vous concernant pouvant documenter un dossier auprès des autorités compétentes pourront être transmises à un industriel afin qu'un plus grand nombre de patients puissent bénéficier des résultats de la recherche. Cette transmission sera faite dans les conditions assurant leur confidentialité.

Vos données pourront être utilisées pour des recherches ultérieures ou des analyses complémentaires à la présente recherche en collaboration avec des partenaires privés ou publics, en France ou à l'étranger, dans des conditions assurant leur confidentialité et le même niveau de protection que la législation européenne.
Vous pouvez vous opposer à tout moment votre consentement à l'utilisation ultérieure de vos données auprès du médecin qui vous suit dans le cadre de cette recherche.

Vos données ne seront conservées que pour une durée strictement nécessaire et proportionnée à la finalité de la recherche. Elles seront conservées dans les systèmes d'information du responsable de traitement jusqu'à *deux ans après la dernière publication des résultats de la recherche.*

Vos données seront ensuite archivées selon la réglementation en vigueur.

Le fichier informatique utilisé pour cette recherche est mis en œuvre conformément à la règlementation française (loi Informatique et Libertés modifiée) et européenne (au Règlement Général sur la Protection des Données -RGPD), Vous disposez d'un droit d'accès, de rectification et d'opposition .au traitement des données couvertes par le secret professionnel utilisées dans le cadre de cette recherche. Ces droits s'exercent auprès du médecin en charge de la recherche qui seul connaît votre identité (identifié en première page du présent document).

Si vous décidez d'arrêter de participer à la recherche, les données recueillies précédemment à cet arrêt seront utilisées conformément à la réglementation, et exclusivement pour les objectifs de cette recherche. En effet, leur effacement serait susceptible de compromettre la validité des résultats de la recherche. Dans ce cas, vos données ne seront absolument pas utilisées ultérieurement ou pour une autre recherche.

En cas de difficultés dans l'exercice de vos droits, vous pouvez saisir le Délégué à la Protection des données de l'AP-HP à l'adresse suivante : protection.donnees.dsi@aphp.fr, qui pourra notamment vous expliquer les voies de recours dont vous disposez auprès de la CNIL. Vous pouvez également exercer votre droit à réclamation directement auprès de la CNIL (pour plus d'informations à ce sujet, rendez-vous sur le site www.cnil.fr).

11) Comment cette recherche est-elle encadrée ?

L'AP-HP a pris toutes les mesures pour mener cette recherche conformément aux dispositions du Code de la Santé Publique applicables aux recherches impliquant la personne humaine.

L'AP-HP a souscrit une assurance (N° d'adhésion 0100518814033 190120) garantissant sa responsabilité civile et celle de tout intervenant auprès de la compagnie HDI–GERLING par l'intermédiaire de BIOMEDICINSURE dont l'adresse est Parc d'Innovation Bretagne Sud C.P.142 56038 Vannes Cedex.

L'AP-HP a obtenu l'avis favorable du Comité de Protection des Personnes pour cette recherche CPP Ile de France III le *06/11/2019*

12) Quels sont vos droits ?

Votre participation à cette recherche est entièrement libre et volontaire. Votre décision n'entraînera aucun préjudice sur la qualité des soins et des traitements que vous êtes en droit d'attendre.

Vous pourrez tout au long de la recherche demander des informations concernant votre santé ainsi que des explications sur le déroulement de la recherche au médecin qui vous suit.

Vous pouvez vous retirer à tout moment de la recherche sans avoir à donner de justification, sans conséquence sur la suite de votre traitement ni la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre médecin. A l'issue de ce retrait, vous pourrez être suivi par la même équipe médicale. Dans ce cas, les données collectées jusqu'au retrait seront utilisées pour l'analyse des résultats de la recherche.

Votre dossier médical restera confidentiel et ne pourra être consulté que sous la responsabilité du médecin s'occupant de votre traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par l'AP-HP pour la recherche et soumises au secret professionnel.

A l'issue de la recherche et après analyse des données relatives à cette recherche, vous pourrez être informé(e) des résultats globaux en le demandant au médecin qui vous suit dans le cadre de cette recherche

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.

Après avoir lu toutes ces informations, discuté tous les aspects avec votre médecin et après avoir bénéficié d'un temps de réflexion, si vous acceptez de participer à la recherche vous devrez signer et dater le formulaire de consentement éclairé se trouvant à la fin de ce document.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

FORMULAIRE DE CONSENTEMENT

Je soussigné(e), M^me^, M. *[rayer les mentions inutiles]* (*nom, prénom*)…….. **accepte librement de participer à la recherche intitulée « utilisation restrictive de la contention physique et durée du délirium en réanimation: essai contrôlé randomisé. R2D2-ICU»** organisée par l'Assistance Publique-Hôpitaux de Paris et qui m'est proposée par le Docteur/Professeur (*nom, prénom, téléphone*) ……, médecin dans cette recherche.

- J'ai pris connaissance de la note d'information version 2.0 du 29/07/2022*[4 pages]* m'expliquant l'objectif de cette recherche, la façon dont elle va être réalisée et ce que ma participation va impliquer,
- je conserverai un exemplaire de la note d'information et du consentement,
- j'ai reçu des réponses adaptées à toutes mes questions,
- j'ai disposé d'un temps suffisant pour prendre ma décision,
- j'ai compris que ma participation est libre et que je pourrai interrompre ma participation à tout moment, sans encourir la moindre responsabilité et préjudice pour la qualité des soins qui me seront prodigués,
- j'ai été informé(e) que les données recueillies dans le cadre de la recherche peuvent être réutilisées pour des recherches ultérieures, et que je pouvais m'y opposer à tout moment
- je suis conscient(e) que ma participation pourra aussi être interrompue par le médecin si besoin, il m'en expliquera les raisons,
- j'ai compris que pour pouvoir participer à cette recherche je dois être affilié(e) à un régime de sécurité sociale ou bénéficiaire d'un tel régime. Je confirme que c'est le cas,
- j'ai bien été informé(e) que ma participation à cette recherche durera 3 mois,
- mon consentement ne décharge en rien le médecin qui me suit dans le cadre de la recherche ni l'AP-HP de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi.

Signature de la personne participant à la recherche		**Signature du médecin**	
Nom Prénom :		Nom Prénom :	
Date :	Signature :	Date :	Signature :

Ce document est à réaliser en 3 exemplaires, un exemplaire doit être conservé 15ans par l'investigateur, le deuxième remis à la personne donnant son consentement et le troisième transmis à l'AP-HP sous enveloppe scellée à la fin de la recherche.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Utilisation restrictive de la contention physique et durée du délirium en réanimation: essai contrôlé randomisé. R2D2-ICU

Cette recherche est promue par l'Assistance Publique - Hôpitaux de Paris
Représentée par la Directrice de la
Délégation à la Recherche Clinique et à l'Innovation
1 avenue Claude Vellefaux
75010 Paris

NOTE D'INFORMATION - PROCHE N°2

Madame, Monsieur,

Le Docteur/ Le Professeur …… (nom, prénom), exerçant à l'hôpital ……, propose à Mme, M. (barrer les mentions inutiles) …… (nom, prénom), de participer à une recherche concernant son état de santé.

En raison de son état qui le/la rend incapable d'exprimer son consentement, et conformément à la loi, c'est à vous, compte tenu des relations que vous entretenez avec lui/elle, que nous demandons l'autorisation de participation à cette recherche.

Il est important de lire attentivement cette note avant de prendre votre décision ; n'hésitez pas demander des explications.
Si vous décidez de la participation de votre proche à cette recherche, un consentement écrit vous sera demandé.

1) Quel est le but de cette recherche ?

Les patients admis en réanimation peuvent souffrir d'agitation, ce qui est associé à une augmentation de la durée de ventilation mécanique et de séjour en réanimation. En effet, cette agitation peut conduire à l'arrachement des dispositifs médicaux comme les sondes urinaires et les perfusions. Afin de prévenir ces auto-arrachements, le personnel médical peut avoir recours à la contention physique.
La contention physique est définie comme l'utilisation des procédés qui empêchent ou limitent les capacités de mouvement volontaire pour protéger une personne d'un comportement estimé dangereux ou mal adapté.
Il n'existe aucune recommandation quant à la contention physique des patients admis en réanimation et bien que fréquemment utilisée, le bénéfice de la contention physique n'est pas clairement établi et pourrait même être délétère, c'est-à-dire nocif, dans ce contexte. Il n'existe, en effet aucune relation démontrée entre le nombre d'auto-arrachements des dispositifs médicaux et le nombre de contentions physiques. Il existe cependant une relation complexe entre l'agitation, la dysfonction cérébrale aiguë (que les anglo-saxons appellent delirium) et contention physique. Alors que la contention physique est mise en place pour éviter les risques potentiels liés à l'agitation, elle semble favoriser le délirium.

Le délirium ou syndrome confusionnel aigu est un terme générique pour définir un changement rapide de l'état mental (de quelques minutes à quelques jours) qui associe des troubles qui fluctuent au cours de la journée : une altération de la conscience avec une diminution de la capacité à fixer son attention, une modification du fonctionnement cognitif (désorganisation de la pensée, trouble de la mémoire) et/ou une perturbation des perceptions non expliquée par des troubles mentaux préexistants. L'expression du délirium peut se manifester par de l'agitation.

Le délirium est un problème fréquent chez les patients admis en réanimation. La contention physique est reconnue comme un facteur majeur de sa survenue, cette recherche porte sur l'effet de la contention physique sur la durée du délirium chez les patients hospitalisés en réanimation et sous ventilation mécanique. Pour répondre à la question posée dans la recherche, il est prévu d'inclure 422 patients dans quelques services de réanimation des établissements de soins participants situés en France.

2) En quoi consiste la recherche ?

Dans la recherche proposée, nous allons comparer, chez des patients ayant une prescription de contention physique comme votre proche, la durée du délirium chez des patients pour lesquels la contention physique est utilisée de manière systématique et chez des patients pour lesquels son utilisation sera limitée à des périodes d'agitation extrême. Après accord de votre part et signature du formulaire de consentement, l'une des deux stratégies vous sera attribuée par tirage au sort. Votre proche sera soit dans le groupe pour lequel la contention physique sera appliquée de manière systématique, soit dans le groupe pour lequel la contention physique ne sera appliquée qu'en cas de période de forte agitation.

3) Quel est le calendrier de la recherche

La durée prévisionnelle de la recherche est de 41 mois et la participation de votre proche sera de 3 mois. Après son inclusion dans l'étude, lors de la première visite, le déroulement de la recherche sera le suivant : votre proche sera suivi(e) quotidiennement pendant 14 jours selon les pratiques de soin habituelles pour sa pathologie ou jusqu'à sa sortie de réanimation si il/elle sort avant J14.
Une visite avec un psychologue sera réalisée 90 jours après son inclusion dans l'étude. Lors de cette visite votre proche devra répondre à différents questionnaires ayant pour but d'évaluer sa force musculaire, ses capacités cognitives (mémoire, réflexion…), son état psychologique, sa qualité de vie ainsi que son parcours de soin (visite chez le médecin, hospitalisation…) depuis sa sortie de réanimation. S'il ne peut pas venir pour cette consultation, il sera joint par téléphone afin de recueillir les informations concernant sa qualité de vie depuis votre sortie de réanimation.

4) Quels sont les bénéfices liés à la participation de votre proche ?

En participant à cette recherche, votre proche bénéficiera d'un suivi médical étroit et spécifique pour lequel aucun frais supplémentaire ne lui sera demandé. Il/elle aura une chance sur deux d'éviter la contention physique systématique qui est appliquée dans le traitement courant des patients atteints de sa pathologie.
Par ailleurs, il contribuera à une meilleure connaissance du recours à la contention physique chez les patients admis en réanimation et sous ventilation mécanique sur la durée du délirium.

5) Quels sont les risques et les contraintes prévisibles ajoutés par la recherche?

Aucun acte spécifique ne sera ajouté par la recherche comparativement aux soins habituels, il n'y a pas de risque supplémentaire par rapport à votre prise en charge habituelle.

Si vous acceptez que votre proche participe, vous devrez veiller à ce qu'il/elle respecte les points suivants :

- Ne pas prendre part à un autre projet de recherche sans l'accord de son médecin, ceci pour le/la protéger de tout accident possible pouvant résulter par exemple d'incompatibilités possibles entre les thérapeutiques étudiées ou d'autres dangers
- Venir au rendez-vous. En cas d'impossibilité, nous vous remercions de contacter son médecin le plus rapidement possible.
- Répondre aux questionnaires posés dans le cadre de l'étude, soit en face à face, soit par téléphone
- Etre affilié(e) à un régime de sécurité sociale ou être bénéficiaire d'un tel régime.

6) Quelles sont les modalités de prise en charge médicale à la fin de la participation de votre proche ?

Votre prise en charge médicale à la fin de votre participation sera strictement la même que dans le cadre de votre prise en charge habituelle. Le médecin pourra décider à tout moment de l'arrêt de la participation de votre proche ; il vous en expliquera les raisons.

7) Si votre proche participe, comment vont être traitées les données recueillies pour la recherche ?

Dans le cadre de la recherche à laquelle l'AP-HP propose à votre proche de participer, un traitement de ses données personnelles va être mis en œuvre pour permettre d'en analyser les résultats de la recherche au regard de l'objectif de cette dernière qui vous a été présenté.

Ce traitement est nécessaire à la réalisation de la recherche qui répond à la mission d'intérêt public dont est investie l'AP-HP en tant qu'établissement public de santé hospitalo-universitaire.

A cette fin, les données médicales le/la concernant et les données relatives à ses habitudes de vie, seront transmises au Promoteur ou aux personnes ou partenaires agissant pour son compte, en France. Ces données seront identifiées par un numéro d'enregistrement. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Les données médicales de votre proche pouvant documenter un dossier auprès des autorités compétentes pourront être transmises à un industriel afin qu'un plus grand nombre de patients puissent bénéficier des résultats de la recherche. Cette transmission sera faite dans les conditions assurant leur confidentialité.

Les données de votre proche pourront être utilisées pour des recherches ultérieures ou des analyses complémentaires à la présente recherche en collaboration avec des partenaires privés ou publics, en France ou à l'étranger, dans des conditions assurant leur confidentialité et le même niveau de protection que la législation européenne.

Vous pouvez vous opposer à tout moment votre consentement à l'utilisation ultérieure de ses données auprès du médecin qui suit votre proche dans le cadre de cette recherche.

Les données ne seront conservées que pour une durée strictement nécessaire et proportionnée à la finalité de la recherche. Elles seront conservées dans les systèmes d'information du responsable de traitement jusqu'à deux ans après la dernière publication des résultats de la recherche.

Les données seront ensuite archivées selon la réglementation en vigueur.

Le fichier informatique utilisé pour cette recherche est mis en œuvre conformément à la règlementation française (loi Informatique et Libertés modifiée) et européenne (au Règlement Général sur la Protection des Données -RGPD), Vous disposez d'un droit d'accès, de rectification et d'opposition au traitement des données couvertes par le secret professionnel utilisées dans le cadre de cette recherche. Ces droits s'exercent auprès du médecin en charge de la recherche qui seul connaît son identité (identifié en première page du présent document).

Si vous décidez d'arrêter sa participation à la recherche, les données recueillies précédemment à cet arrêt seront utilisées conformément à la réglementation, et exclusivement pour les objectifs de cette recherche. En effet, leur effacement serait susceptible de compromettre la validité des résultats de la recherche. Dans ce cas, ses données ne seront absolument pas utilisées ultérieurement ou pour une autre recherche.

En cas de difficultés dans l'exercice de vos droits, vous pouvez saisir le Délégué à la Protection des données de l'AP-HP à l'adresse suivante : protection.donnees.dsi@aphp.fr, qui pourra notamment vous expliquer les voies de recours dont vous disposez auprès de la CNIL. Vous pouvez également exercer votre droit à réclamation directement auprès de la CNIL (pour plus d'informations à ce sujet, rendez-vous sur le site www.cnil.fr).

11) Comment cette recherche est-elle encadrée ?

L'AP-HP a pris toutes les mesures pour mener cette recherche conformément aux dispositions du Code de la Santé Publique applicables aux recherches impliquant la personne humaine.

L'AP-HP a souscrit une assurance (N° d'adhésion 0100518814033 190120) garantissant sa responsabilité civile et celle de tout intervenant auprès de la compagnie HDI–GERLING par l'intermédiaire de BIOMEDICINSURE dont l'adresse est Parc d'Innovation Bretagne Sud C.P.142 56038 Vannes Cedex.

L'AP-HP a obtenu l'avis favorable du Comité de Protection des Personnes pour cette recherche CPP Ile de France III le 06/11/2019.

12) Quels sont les droits de votre proche?

La participation de votre proche à cette recherche est entièrement libre et volontaire. Votre décision n'entraînera aucun préjudice sur la qualité des soins et des traitements qu'il/elle est en droit d'attendre.

Vous pourrez tout au long de la recherche demander des informations concernant la santé de votre proche ainsi que des explications sur le déroulement de la recherche au médecin qui le/la suit.

Vous pouvez retirer à tout moment la participation de votre proche à la recherche sans avoir à donner de justification, sans conséquence sur la suite de son traitement ni la qualité des soins qui lui seront fournis et sans conséquence sur la relation avec son médecin. A l'issue de ce retrait, il/elle pourra être suivi par la même équipe médicale. Dans ce cas, les données collectées jusqu'au retrait seront utilisées pour l'analyse des résultats de la recherche.

Le dossier médical de votre proche restera confidentiel et ne pourra être consulté que sous la responsabilité du médecin s'occupant de son traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par l'AP-HP pour la recherche et soumises au secret professionnel.

A l'issue de la recherche et après analyse des données relatives à cette recherche, vous pourrez être informé(e) des résultats globaux en le demandant au médecin qui suit votre proche dans le cadre de cette recherche

Vous pouvez également accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de ses données médicales en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.

Après avoir lu toutes ces informations, discuté tous les aspects avec le médecin et après avoir bénéficié d'un temps de réflexion, si vous acceptez que votre proche participe à la recherche vous devrez signer et dater le formulaire de consentement éclairé se trouvant à la fin de ce document.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

FORMULAIRE DE CONSENTEMENT

Je soussigné(e), Mme, M. *[rayer les mentions inutiles]* (*nom, prénom*)……...
accepte librement en qualité de personne de confiance*, proche, parent** *[rayer les mentions inutiles]*
que Mme, M. *[rayer les mentions inutiles]* (*nom, prénom*)…….. **participe à la recherche intitulée** « **R2D2- ICU** » organisée par l'Assistance Publique - Hôpitaux de Paris et qui m'est proposée par le Docteur/Professeur/Personne qualifiée (*nom, prénom, téléphone*) ……, médecin dans cette recherche.

- J'ai pris connaissance de la note d'information version 2.0 du 29/07/2022 *[4 pages]* m'expliquant l'objectif de cette recherche, la façon dont elle va être réalisée et ce que la participation de mon/ma proche va impliquer,
- je conserverai un exemplaire de la note d'information et du consentement,
- j'ai reçu des réponses adaptées à toutes mes questions,
- j'ai disposé d'un temps suffisant pour prendre ma décision,
- j'ai compris que la participation de mon/ma proche est libre et que je pourrai interrompre sa participation à tout moment, sans encourir la moindre responsabilité et préjudice pour la qualité des soins qui lui seront prodigués.
- j'ai été informé(e) que les données recueillies dans le cadre de la recherche peuvent être réutilisées pour des recherches ultérieures, et que je pouvais m'y opposer à tout moment
- je suis conscient(e) que la participation de mon/ma proche pourra aussi être interrompue par le médecin si besoin, il m'en expliquera les raisons,
- j'ai compris que pour pouvoir participer à cette recherche, mon/ma proche doit être affilié(e) à un régime de sécurité sociale ou bénéficiaire d'un tel régime. Je confirme que c'est le cas,
- j'ai bien été informé(e) que la participation de mon/ma proche à cette recherche durera 3 mois,
- mon consentement ne décharge en rien le médecin qui le/la suit dans le cadre de la recherche ni l'AP-HP de l'ensemble de leurs responsabilités et mon/ma proche conserve tous ses droits garantis par la loi.

Une information de l'intéressé(e) doit également être effectuée, adaptée à sa capacité de compréhension et à son état. Son adhésion pour la participation à cette recherche est sollicitée et il ne peut être passé outre à son refus ou à la révocation de son acceptation.

Les deux personnes qui signent ce document attestent que c'est bien le cas.

Signature de la personne donnant l'accord de participation à la recherche		**Signature du médecin**	
Nom Prénom : Lien avec l'intéressé(e) :		Nom Prénom :	
Date :	Signature :	Date :	Signature :

*** La personne de confiance doit avoir été désignée au préalable par écrit, par le patient (art. L.1111-6 du CSP)**
**** le Proche : personne entretenant des liens étroits et stables avec l'intéressé(e) (art. L.1122-2 II 6e alinéa)**

Ce document est à réaliser en 3 exemplaires, un exemplaire doit être conservé 15 ans par l'investigateur, le deuxième remis à la personne donnant son consentement et le troisième transmis à l'AP-HP sous enveloppe scellée à la fin de la recherche.

Restrictive use of Restraints and Delirium Duration in the Intensive Care Unit (R2D2-ICU): Statistical Analysis Plan for a Multicentre Parallel-group Open Label Randomized Controlled Trial

Table

1 Endpoints

Endpoints will be compared between randomization groups (restrictive use of PR vs. systematic use of PR).

1.1 Primary endpoint

It will be the number of delirium-free or coma-free days, defined as the number of days in the first 14 days after randomization during which the patient was alive without delirium or not in coma from any cause. This endpoint will be assessed twice a day by the French validated translation of the Richmond Agitation Sedation Score (RASS) and CAM-ICU by well-trained nurses. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score > or = -3 will be assessed for delirium with the use of the CAM-ICU scale.

1.2 Secondary endpoints

1.2.1 Delirium duration until ICU discharge

This criterion is defined by the number of days on delirium until ICU discharge, the proportion of positive CAM-ICU until ICU discharge.

1.2.2 Incidence of delirium between D0 and D14

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 and D14.

1.2.3 Incidence of delirium until ICU discharge

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 until ICU discharge.

1.2.4 Agitation duration between D0 and D14

This criterion is defined by the number of days alive with agitation (RASS ≥ 2) between D0-D14.

1.2.5 Exposure to analgesic (opioids) between D0 and D14

This criterion is defined by the total cumulative dose of opiod analgesics (and subclass of opioids) between D0 and D14.

1.2.6 Exposure to propofol between D0 and D14

This criterion is defined by the total cumulative dose of propofol between D0 and D14.

1.2.7 Exposure to benzodiazepines between D0 and D14

This criterion is defined by the total cumulative dose of benzodiazepines as anxiolytic between D0 and D14.

1.2.8 Exposure to antipsychotic agents between D0 and D14

This criterion is defined by the total cumulative dose of antipsychotics agents (Haloperidol, Levomepromazine and Cyamemazine) between D0 and D14.

1.2.9 Exposure to dexmetomidine between D0 and D14

This criterion is defined by the total cumulative dose of dexemtomidine between D0 and D14

1.2.10 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

This criterion is defined by the total number of hours without mechanical ventilation between D0 and D14.

1.2.11 Patient mobility according to the visual global mobilisation score between D0 and D14

This criterion is defined by the Median of Mobilisation capacity and rate of patients > 2 on a visual scale ranging from 0 (no mobilisation) to 4 (ambulation) between D0- D14.

1.2.12 Incidence of self-extubation and device removal between D0 and D14

This criterion is defined by the rate of patients with at least one self-extubation or any device removal (Central catheter, arterial catheter or urinary catheter) between D0 and D14.

1.2.13 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

This criterion is defined by the rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel between D0-D14 (at least one ulcer of grade III or IV per patient).

1.2.14 ICU and hospital lengths of stay

This criterion is defined by the number of hospitalization day.

1.2.15 In-ICU and in-hospital mortality

This criterion is defined by the mortality rate on ICU stay and during hospitalization.

1.2.16 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

This criterion is defined by:

- The rate of patients with at D90 an altered cognitive capability defined as a MMSE (Mini Mental State Examination) ≤ 24 points
- The rate of patients with a frontal syndrome defined as a FAB (Frontal Assessment Battery at Bedside) < 15 points
- The rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder (PTSD) defined as a R-IES (Revised-Impact of events scale) ≥ 33 points
- The rate of patients with a functional disability defined as a GOS-E (Glasgow Outcome Scale – Extended) ≤ 6 points
- The rate of patients with functional independence, evaluated by the FIM (Functional Independence Measurement)

2 General considerations

2.1 Flowchart

A flowchart following *Consolidated Standards of Reporting Trials (CONSORT)* standards, describing patients flow throughout the study, included and randomized, will be provided. The flowchart will specify the number of patients in each arm and describe loss of patients during the study.

2.2 Level of statistical significance

In this study, the statistical level of significance (Type I error) will be fixed at 5%.

2.3 First day of patient- follow-up (D0)

The first day of patient follow-up (D0) is the day of randomization. This day is the reference day which will be used as the initial date in the calculation of all delays.

3 Statistical analysis

3.1 Descriptive analysis

The variables that will be described are as follows:

- Comorbidities/Demographic data of the included population and at ICU admission
- Treatments administred at ICU admission (Ketamine, Etomidate, Propofol and others)
- Clinical and biological data at ICU admission and from D1 to D14
- Clinical scores at ICU admission and from D1 to D14

- End-of-study data/Discharge assessment
- Clinical scores at D90

The dedicated score to assess the delirium-free and coma-free days will be described per day – morning and evening assessment. A time plot will be provided to allow a graphical description of the quality assessment between D0 and D14. Melatonin exposure will be described per day and on total, with normalization on number of days on ICU to allow patients discharged before D14 to be taken into account.

All qualitative variables will be described by their number and corresponding frequency. Quantitative variables will be described by their min and max, mean and standard deviation, median, Q1 and Q3. For each variable, the number and frequency of missing data will be reported.

The description will be made for all patients and then according to the randomisation group (systematic PR vs. restrictive PR). The total number of patients and in each group will be specified. Melatonin exposure description will be also made according to the use of different devices in the medical room (i.e. earplugs, masks, natural light).

Results of descriptive analysis will be presented in tables as follows:

	Total population (N=)	Systematic PR (N=)	Restrictive PR (N=)
Quantitative variable			
	Range	Range	Range
	Median [IQR]	Median [IQR]	Median [IQR]
	Mean (SD)	Mean (SD)	Mean (SD)
	NA (n (%))	NA (n (%))	NA (n (%))
Qualitative variable			
« First modality »	% (n/N)	% (n/N)	% (n/N)
« Second modality »	% (n/N)	% (n/N)	% (n/N)
Missing	% (n/N)	% (n/N)	% (n/N)

3.2 Analysis of the primary endpoint

Analysis set

The main analysis will be in intent to treat (ITT), that is, patients will be analyzed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analyzed in the arm of management actually received.

Descriptive statistics and graphical representation

Results of CAM-ICU (Positive/Negative/Not done) will be described each day and for each evaluation, with sample size and proportion of patients in each modality, from D0 to D14, on total population and according to the randomisation group.

We will construct a variable summarizing CAM-ICU results each day (Morning CAM-ICU positive and evening CAM-ICU negative/Morning CAM-ICU negative and evening CAM-ICU positive/Both morning and evening CAM-ICU positives/Both morning and evening CAM-ICU negatives) from D0 to D14. This variable will be described with sample size and proportion of patient in each modality, from D0 to D14, on total population and according to the randomisation group.

The number of patients without coma and delirium will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The number of delirium-free and coma-free days will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made for all patients and then according to the randomisation group.

Statistical methodology

A variable corresponding to the number of delirium-free and coma-free days between D0 and D14 (primary endpoint) will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where all CAM-ICU evaluations (morning, evening or supplementary CAM-ICU evaluations) are negative. Each day, from D0 to D14, primary endpoint for ICU discharged patients will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days will be considered days of coma.

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all RASS or CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by days with coma.
- If there are non-missing data before and after the missing data and data before missing data show RASS ≥ -3 (patient not considered comatose), missing result will be imputed by days without coma.
- It will be considered that a delirium day cannot be a coma day and vice versa, meaning that in case of days with RASS ≤ -4 (patient considered comatose), and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value and in case of days with positive CAM-ICU and missing RASS, RASS results are imputed by no coma days.
- In case of missing data until D14, a last value carried forward imputation method will be performed, for both RASS and CAM-ICU

The number of coma or delirium free days between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon text as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3 Analyses of secondary endpoints

3.3.1 Delirium duration until ICU discharge

Analysis set

This analysis will be performed on the sub-population of patients having at least one day of delirium between D0 and D14.

Descriptive statistics and graphical representation

The number of days with delirium (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The proportion of positive CAM-ICU until ICU discharge will be described using frequencies, on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The number of CAM-ICU performed until ICU discharge will be constructed for each patient. This variable will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

Statistical methodology

The number of days with delirium will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where at least one of the morning, evening or supplementary CAM-ICU evaluations is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value
- In case of missing data until D14, a last value carried forward imputation method will be performed

Number of days with delirium between D0 and D14 will be compared between randomisation group using Student’s t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

The proportion of positive CAM-ICU until ICU discharge will be compared between randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test. Proportions of positive CAM-ICU will be presented with 95% confidence intervals according to the randomisation group.

The number of CAM-ICU performed until ICU discharge will be compared between randomisation group using Student’s t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.2 Incidence of delirium between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with delirium (constructed variable, see below) will be described each day, between D0 and D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

Patients with delirium between D0 and D14 are defined as patients experiencing delirium at least one day from D0 to D14, a delirium day being a day with at least one of the morning, evening or supplementary CAM-ICU evaluations that is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.

- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value.
- In case of missing data until D14, a last value carried forward imputation method will be performed

Rate of patients with delirium between D0 and D14 will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients with delirium between D0 and D14 with 95% confidence intervals and according to the randomisation group.

3.3.3 Agitation duration between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The number of days with agitation (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

The number of days with agitation between D0 and D14 will be a constructed variable, indicating for each patient the total amount of days where the patient is alive with RASS ≥ 2. Imputation methods for this endpoint are as follows:

- If the patient is discharged before D14, after extubation, the remaining days are considered no agitation days.
- If the patient is discharged before D14, always in MV, the remaining days are considered agitation days.

- If the patient dies within 14 days, the number of non-surviving days are considered as no agitation days.

In case of partial missing RASS evaluation (i.e. at least one of the morning, evening or supplemental RASS evaluation is not missing), we will impute the missing RASS evaluation by the non-missing evaluation of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with days with total missing RASS evaluation, we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by coma days (i.e. RASS ≤ -4).
- In case of missing data until D14 for RASS score, a last value carried forward imputation method will be performed

The number of days with agitation between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3.4 Exposure to analgesic (opioids) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Doses of analgesic (opioids) will be described each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Total cumulative dose of analgesic (opioids) from D0 to D14 will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. Total cumulative doses of analgesic (opioids) between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.5 Exposure to propofol between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative doses of propofol from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of propofol between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.6 Exposure to benzodiazepines between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative dose of benzodiazepines from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of benzodiazepines between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.7 Exposure to antipsychotic agents between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose from D0 to D14 for each antipsychotic agent (i.e. Haloperidol, Levomepromazine and Cyamemazine) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The same description will be made for total cumulative dose of all antipsychotic agent.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of antipsychotic agents between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.8 Exposure to dexmedetomidine between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose of dexmedetomidine will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical method

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of dexmedetomidine between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.9 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The number of patients exposed to IMV will be described each day, from D0 to D14, using frequencies. The description will be made for the total population and according to the randomisation group. The same description will be made for the number of patients exposed to IMV between D0 and D14.

The total amount of hours under IMV between D0 and D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For invasive mechanical ventilation exposure, it will be considered that:

- If the patient is discharged before D14, after extubation, the remaining days are not considered as days with exposure to invasive mechanical ventilation

- If the patient is discharged before D14, always in MV, the remaining days are considered as days with MV
- If the patient is discharged before D14, not in MV, the remaining days are considered as days without MV
- If the patient dies within 14 days, the remaining days are considered as days with MV

Exposure to IMV will be compared according to the randomisation group using student's t-test or Wilcoxon as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.10 Patient mobility according to the visual global mobilisation score between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The visual global mobilisation score will be descripted each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The visual global mobilisation score will be also descripted for the total D0-D14 period, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The rate of patients with global mobilisation score > 2 will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

Boxplots of the visual global mobilisation score from D0 to D14 will be realized to allow graphical representation of patient mobility.

Statistical methodology

There will be no methods for replacing missing data. The median of the visual mobilisation score on the D0-D14 period will be firstly normalized by the number of days under ICU hospitalization, to allow discharge from ICU or death before D14 to be taken into account. Normalized visual mobilisation score on the D0-D14 period will be compared

between randomisation group using Wilcoxon test. Results will be presented using median and p-value of the test.

3.3.11 Incidence of self-extubation and device removal between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patient experiencing self-extubation will be described for each device (self-extubation, removal of central catheter, arterial catheter or urinary catheter), each day for D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The same description will be realized for self-extubation or any device removal and for any device removal only.

Statistical methodology

The proportion of patients with self-extubation or any device removal will be compared between randomisation groups using chi-squared or Fisher test as appropriate. The same comparison between randomisation groups will be made for patients experiencing self-extubation only and for patients experiencing any device removal only. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.12 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patients with skin lesions will be described for each skin lesion (wrist, heel, sacrum, other), each day from D0 to D14, using frequencies. This description will

be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

The proportion of patients with at least one of the four types of skin lesions (wrist, heel, sacrum, other) will be described, each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

Statistical methodology

The proportion of patients with wrist lesions, the proportion of patients with heel lesions, the proportion of patients with sacrum lesions, and the proportion of patients with other skin lesions between D0 and D14 and according to the randomisation group will be analysed individually using chi-squared or Fisher test as appropriate. Results will be presented using p-value of the tests as well as proportion of patients with each lesion with their 95% interval confidence and according to the randomisation group.

The same analysis will be realized for patients having at least one of the four types of skin lesion (wrist, heel, sacrum, other) between D0 and D14 using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.13 ICU and hospital lengths of stay

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The ICU length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The hospital length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodologyFor patients dying within 14 days, it will be considered that they stayed in ICU and hospital from ICU admission to date of death and from hospital admission to date of death respectively. In case of missing date for ICU discharge or hospital discharge outside patients who died within 14 days, the date of discharge from ICU/hospital will be imputed by the date of the patient's last news.

ICU length of stay and hospital length of stay will be analysed between according to randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.14 In-ICU and in-hospital mortality

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The proportion of dead patients will be described each day, from D0 to D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

To allow lost-to-follow up patients to be taken into account, a Kaplan-Meier model will be realized, the event of interest being in-ICU death or in-hospital death. We will perform a log rank test to compare survival distributions according to the randomisation group. Results will be presented using p value of the log rank test, as well as proportion of death at day 90 between randomisation groups with their 95% interval confidence and according to the randomisation group.

3.3.15 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with altered cognitive capabilities at D90, the rate of patients with a frontal syndrome at D90, the rate of patients with a possible diagnosis of PTSD, the rate of patients with a functional disability at D90 and the rate of patients with a functional independence at D90 will be described using frequencies. These descriptions will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no imputation for missing data. Each individual endpoint will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test as well as proportion of patients with altered cognitive capabilities at D90, proportion of patients with a frontal syndrome at D90, proportion of patients with a possible diagnosis of PTSD, proportion of patients with a functional at D90 and proportion of patients with a functional independence at D90. Each proportion will be provided with their 95% interval confidence and according to the randomisation group.

3.3.16 Center effect, age group effect and presence of coma at beginning of IMV effect

The center effect will be assessed by testing interaction between trial arm and the center in a linear regression modelling the number of delirium-free and coma-free days between D0 and D14. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of IMV. Results will be presented using coefficients of the linear regression with 95% confidence intervals as well as p-value of the tests. In case if significant interaction, a sub-group analysis will be performed.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2.

3.4 Sensitivity analysis

3.4.1 Number of days lived without coma and without delirium for patients leaving ICU before D14

This analysis will consist of a multivariate linear regression predicting the number of days lived without coma and without delirium in the sub-population of patients leaving ICU before D14, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2. Missing values for MV exposure will be imputed using same methodologies as described in §3.3.9. There will be no imputation for sedation time.

3.4.2 Physical restraint exposure

A sensitivity analysis will be performed on primary endpoint for patients whose exposure to either restrictive or systematic RA has been fully respected over the 14 days according to the predefined rules. In addition, an analysis will be carried out on patients who have had no change in their exposure to RA during the 14 days or until discharge from intensive care after extubation.

3.4.3 Sedative exposure at intubation at D0

Sensitivity analysis for the primary endpoint will be performed on the sub-population of patients exposed to sedative agents at intubation at D0.

3.5 Subgroup analysis

3.5.1 Center effect, age group effect and presence of coma at beginning of IMV effect

In case of significant interaction for analyses described in §3.3.16, a sub-group analysis will be performed for the prediction of number of delirium-free and coma-free days between D0 and D14. An ANOVA will be used for comparison of number of delirium-free and coma-free days from D0 to D14 between centres. We will use Student's t-test test or Wilcoxon test as appropriate to compare number of delirium-free and coma-free days from

D0 to D14 between age groups and according to presence of coma at beginning of IMV. Results will be presented using mean or median as appropriate and p-values of the test.

3.5.2 Covid patients

A subgroup analysis will be performed on patients exposed to COVID for the comparison of number of delirium-free and coma-free days between D0 and D14 and according to COVID exposure. We will use Sudent's t-test or Fisher test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

4 Software

Statistical analyses will be made using R v. 4.2.1 or later (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/), or SAS Version 9.4 or later (SAS Institute Inc., Cary,NC).

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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

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ABSTRACT

Introduction Physical restraint (PR) is prescribed in patients receiving invasive mechanical ventilation in the intensive care unit (ICU) to avoid unplanned removal of medical devices. However, it is associated with an increased risk of delirium. We hypothesise that a restrictive use of PR, as compared to a systematic use, could reduce the duration of delirium in ICU patients receiving invasive mechanical ventilation.

Methods and analysis The Restrictive use of Restraints and Delirium Duration in ICU (R2D2-ICU) study is a national multicentric, parallel group, randomized (1:1) open label, controlled, superiority trial which will be conducted in 10 ICUs. A total of 422 adult patients requiring invasive mechanical ventilation for an expected duration of at least 48 hours and eligible to prescription of PR will be randomly allocated within 6 hours from intubation to either the restrictive PR use group or the systematic PR use group, until day 14, ICU discharge or death, whichever comes first. In both groups, PR will consist of the use of wrist straps. The primary endpoint will be delirium or coma-free days, defined as the number of days spent alive in the ICU without coma or delirium within the first 14 days after randomisation. Delirium will be assessed using the CAM-ICU twice daily. Key secondary endpoints will encompass agitation episodes, opioid, propofol, benzodiazepine, and antipsychotic drug exposure during the 14-day intervention period, along with a core outcome set of measures evaluated 90 days post-randomization.

Ethics and dissemination The R2D2-ICU study has been approved by the Comité de Protection des Personnes (CPP) ILE DE FRANCE III – PARIS (CPP19.09.06.37521) on 06/10/2019). Participant recruitment started on January 25th, 2021. Results will be published in international peer-reviewed medical journals and presented at conferences.

Trial registration number NCT05248035, first posted on February 18th, 2020.

STRENGTHS AND LIMITATIONS

- R2D2-ICU is a large multicentre randomized controlled trial evaluating the impact of physical restraint on the duration of delirium among mechanically ventilated patients in the intensive care unit.
- The R2D2-ICU trial evaluates a clinically relevant primary outcome, i.e., the number of delirium or coma-free days within the first 14 days after randomisation.
- The trial includes a 90-day follow-up period to track patient progress and evaluate additional measures beyond the primary outcome.
- Due to the open-label design of the trial, we will standardize the delirium assessment and management in both groups according to international guidelines.

INTRODUCTION

Background and rationale

The application of physical restraint (PR) within intensive care units (ICUs) has been a customary practice aimed at ensuring patient safety and averting the inadvertent removal of medical devices. However, studies have revealed substantial variability in the prevalence of PR use, with rates spanning from 0% to 100% in European ICUs [1]. Patients subjected to PR are more likely to be ventilated, sedated, and managed in larger units with lower nurse-to-patient ratios.

Interestingly, only a minority of ICUs have a written protocol for PR use, underscoring the absence of standardized practices in this field [2]. In a randomised trial of protocolised sedation, PR was utilised in 76% of patients for a median duration of 4 days [3]. Additionally, a survey in French centres disclosed that PR was employed in over 50% of mechanically ventilated patients in 82% of ICUs, with a lack of written local procedures in the majority of cases [4].

The American guidelines on pain, agitation, and delirium management do not give specific recommendations for PR use [5,6]. In a prospective study conducted in 51 ICUs in Canada, treatment characteristics seemed to predict PR use (higher daily doses of benzodiazepines and opioids, antipsychotic drugs, and agitation), as opposed to patient or ICU characteristics [7].

Despite the commonplace application of PR, its benefits in critically ill patients remain unestablished, and it may even be deleterious, by causing injury, agitation, and psychological distress for patients and families. PR has been linked to adverse psychological effects, including stressful memories for survivors of critical illness [8]. Moreover, its complex association with brain dysfunction, manifested as agitation and/or delirium, raises concerns. While PR is intended to mitigate the potential risks associated with agitation, it appears to favour the development of delirium [9]. In a previous study, the risk of use of PR was increased in patients with delirium or coma, in patients who could not communicate verbally, and in patients receiving psychoactive or sedative drugs [2].

Delirium, defined as a disturbance in attention and awareness developing over a short period of time, is common occurrence in critically ill patients receiving invasive mechanical ventilation. It is associated

with poor outcomes, including higher morbidity and mortality [10], and long term cognitive impairment in survivors [11]. Recent research emphasizes the need to better understand delirium mechanistically to facilitate prevention and treatment [12]. In this context, PR may represent a modifiable risk factor for delirium in ICU patients [13,14]. The number of days without delirium in the ICU is significantly associated with both short-term mortality and long-term cognitive impairment, suggesting the potential importance of addressing PR practices in the ICU to improve patient outcomes.

Hypothesis

We hypothesize that a restrictive use of PR, as compared to a systematic use, could reduce the duration of coma and delirium among patients receiving invasive mechanical ventilation (MV) in the ICU.

Objectives

Study objectives and associated endpoints are presented in **Box 1**. The primary objective is to assess whether a restrictive use of PR, as compared to a systematic use, decreases delirium duration during the first 14 days after randomization. The 15 secondary objectives are presented in the **Box 1.**

Box 1 Study objectives and associated endpoints

Primary objective	**Primary endpoint**
To assess whether a restrictive use of PR, in comparison to a systematic use, decreases delirium duration during the first 14 days after randomization.	Delirium or coma-free days, defined by the number of days alive without delirium (measured by CAM-ICU) or coma (measured by RASS) during the first 14 days (D14) after randomization (D0).
Secondary objectives	**Secondary endpoints**
To evaluate the effect of restrictive use of PR between D0 and D14 on: ➢ Incidence of delirium ➢ Agitation duration ➢ Exposure to opioids ➢ Exposure to propofol ➢ Exposure to benzodiazepines ➢ Exposure to antipsychotic agents ➢ Exposure to dexmedetomidine ➢ Exposure to MV ➢ Patient mobility according to the visual mobilisation score ➢ Incidence of self-extubation and device removal ➢ Skin lesions occurrence	➢ percentage of patients with at least one day of delirium (positive CAM-ICU) between D0-D14 ➢ Number of days alive with agitation (RASS score ≥ +2) between D0-D14 ➢ Total cumulative dose of opioids infusion between D0-D14 ➢ Total cumulative dose of propofol infusion between D0-D14 ➢ Total cumulative dose of benzodiazepines infusion between D0-D14 ➢ Total cumulative dose of antipsychotics infusion between D0-D14 ➢ Total cumulative dose of dexmedetomidine infusion between D0-D14 ➢ Invasive mechanical ventilation-free hours between D0-D14 ➢ Median of mobilisation capacity and rate of patients >2 on a visual scale (SOMS) ranging from 0 (no mobilisation) to 4 (ambulation) between D0-D14 ➢ Rate of patients with at least one self-extubation or any device removal between D0-D14 ➢ Rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel (at least one ulcer of grade III or IV per patient) between D0-D14
To evaluate the effect of restrictive use of PR until ICU Discharge on: ➢ Delirium duration until ICU discharge: Patients will be considered "ready for discharge" as soon as all clinical conditions for ICU discharge will be fulfilled ➢ ICU and hospital lengths of stay ➢ In-ICU and in-hospital mortality	➢ Number of days on delirium until ICU discharge ➢ Number of days of ICU stay and of hospital stay [up to D90] ➢ Death rate during ICU stay and hospital stay [up to D90]
To evaluate the effect of restrictive use of PR at D90 (after inclusion) on the global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD)	➢ Rate of patients with altered cognitive capabilities defined as a score on the Mini Mental State Examination ≤ 24 points ➢ Rate of patients with a frontal syndrome defined as a score on the FAB < 15 points ➢ Rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder defined as a score on the IES-R ≥ 33 points ➢ Rate of patients with a functional disability, defined as a score on the GOS-E ≤ 6 points ➢ Functional independence status (yes or no) evaluated on the FIM scale

CAM-ICU: Confusion Assessment Method for Intensive Care Unit; D: Day; FIM Functional Independence Measurement; FAB: Frontal Assessment Battery; GOS-E Glasgow Outcome Scale-Extended; IESR: Impact of Events Scale-Revised; MV: Mechanical Ventilation; RASS Richmond Agitation Sedation Scale.

METHODS AND ANALYSIS

Design overview

The R2D2-ICU study is an investigator-initiated, national multicentric, superiority, open label parallel-group, comparative controlled randomized trial, in which patients being on invasive MV in the ICU for a duration inferior to 6 hours are allocated in a 1:1 ratio to restrictive PR use group (intervention group) or to systematic PR use group (control group). The trial design is summarised in **table 1** and in **figure 1**. We report the study protocol according to the Standard Protocol Items: Recommendations for Interventional Trials statement (**supplementary material 1**) [15]. The selection of a parallel group design, randomised with two interventions, one of which includes systematic PR, allows for the elimination of service-specific practices, and focuses on patient-centred considerations. The practice guidelines outlined in the protocol for each group will facilitate standardised management, thereby minimising the risk of cross-contamination. 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.

Patient inclusion and randomization will be conducted either by the principal investigator or by a physician representing the investigator. Patient eligibility will be assessed in accordance with the predefined inclusion and exclusion criteria. 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.

Each centre will maintain a screening log for all eligible patients. The use of physical restraint will involve the use of wrist straps, precluding a blind investigation of group assignments. The observation period for patients will extend from the time of inclusion until their discharge from the ICU or until their demise, with a specific follow-up consultation scheduled at day 90 for all surviving patients.

Table 1. Summary study data collected

Timepoints	Screening D0	Randomisation D0	D1 to D14	Discharge	D90
Description of timepoints	Within 6 hours after beginning of invasive MV		0 to 14	Day of ICU and hospital discharge	90 days after randomization
Eligibility screen	X	X			
Informed consent*		X			
SAPS2	X	X			
SOFA	X	X			
Admission variables		x			
Demographics		x			
Comorbid conditions		x			
Drug/alcohol consumption		X			
Benzodiazepine treatment		X			
Cognitive impairment		X			
Braden scale		X			
BPS		X	X		
SARS-CoV-2 status	X				
Main reason of IMV		X			
Outcome variables					
RASS (twice a day)		X	X		
CAM-ICU (twice a day)		X	X		
Sedatives (propofol, benzodiazepines, and dexmedetomidine)			X		
Opioids			X		
Antipsychotics			X		
Agitation					
Self-extubation			X		
Accidental removal of medical devices			X		
Mobilization by visual scale			X		
Skin lesions			X		
Length of stay (ICU and Hospital)			X	X	X
Vital status			X	X	X
Follow-up consultation (mRS, MRC, MMS-E, FAB, IES-R, GOS-E, FIM, IPREA scales)					X

MV Mechanical ventilation; RASS Richmond Agitation Sedation Scale; CAM-ICU Confusion Assessment Method for the ICU; MMSE Mini Mental State Evaluation; FAB Frontal Assessment Battery; IES-R Impact of Events Scale-revised; IPREA Inconforts des Patients de REAnimation; GOS-E Glasgow Outcome Scale-Extended; FIM Functional Independence Measure; MRC Medical Research Council Scale; ICU Intensive Care Unit; SAPS2 Simplified Acute Physiology Score 2; SOFA Sequential Organ Failure Assessment; BPS behavioral pain scale; MV mechanical ventilation.

* Not mandatory, emergency inclusion is authorized by the French authorities. In case of emergency inclusion, close relative and/or patient written informed consents will be collected as soon as possible.

Interventions

For all patients, PR will consist of the use of wrists straps. The restrictive or systematic strategies will be applied until one of the following events occur, whichever comes first: a) day 14 in ICU; b) ready for "ICU discharge" (Patients will be considered "ready for discharge" as soon as all clinical conditions for ICU discharge will be fulfilled (i.e., no more need for vital-organ support, and no more need for central or arterial catheter); c) death before day 14. 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 for details).

Intervention group

In the restrictive PR use group, patients will be subjected to PR only in case of severe agitation, defined by a RASS score ≥ +3 on any given day between day 0 and day 14.

Control group

In the systematic PR use group, patients will be systematically subjected to PR, which will be re-evaluated every day every day between day 0 and day 14. The removal of PR will be allowed when patients meet any of the following criteria: 1) Awake without delirium, defined by a RASS > -4 and a negative CAM-ICU; 2) Extubated without delirium, defined by the absence of invasive MV and a negative CAM-ICU. The PR will be resumed in case of severe agitation, defined by a RASS ≥ +3 on any given day between day 0 and day 14, irrespective of the need for invasive MV.

Study setting and population

Patients will be prospectively recruited among patients admitted in 10 French ICUs. Patients will be considered eligible for enrolment if they fulfil the inclusion criteria and none of the exclusion criteria, as defined in **Box 2**. A flow diagram of the R2D2-ICU trial is presented in **figure 1**.

Box 2 Eligibility criteria

Inclusion criteria

- ✓ Adult ≥ 18 years
- ✓ Invasive mechanical ventilation expected for at least ≥ 48 hours
- ✓ Invasive mechanical ventilation in the ICU for a duration inferior to 6 hours
- ✓ Eligible to physical restraint prescription*

Exclusion criteria

- ✓ Documented delirium prior to ICU admission according to the CAM-ICU
- ✓ History of dementia (Mini mental test < 24)
- ✓ Alcohol withdrawal syndrome expected
- ✓ Admission for any neurological disease including post-cardiopulmonary resuscitation (cardiac arrest, stroke, traumatic brain injury, meningoencephalitis, and status epilepticus)
- ✓ Serious auditory or visual disorders
- ✓ Unable to understand French
- ✓ Pregnant or lactating women
- ✓ SAPS II > 65 points at screening
- ✓ Do-not-resuscitate orders
- ✓ No affiliation to a social security regime (beneficiary or assignee)
- ✓ Patient or person of confidence (if present at the time of inclusion) opposing the patient's participation in research
- ✓ Patient already involved in another interventional clinical research whose main objective is related to delirium

ICU: Intensive Care Unit; CAM ICU Confusion Method Assessment in the ICU; SAPS2: Simplified Acute Physiology Score 2.

*Not already restrained because of a previous written medical prescription.

Outcomes

Primary endpoint

The primary endpoint is delirium or coma-free days, defined by the number of days alive without delirium (measured by CAM-ICU) or coma (measured by RASS) during the first 14 days after randomization. Brain dysfunction in the ICU, i.e., delirium or coma, is serious event in critically ill patients that is associated with prolonged hospital stays, costs, increased mortality, and cognitive impairment in survivors. In this regard, the number of days alive without delirium or coma in the ICU has emerged as a clinically relevant endpoint in critical care trials [16,17]. Moreover, duration of delirium in the ICU is associated with important patient-centred outcomes, including worse global cognition and executive function at 12 months following ICU discharge [18].

This endpoint will be assessed twice daily if needed according to patients' clinical status by the French validated translation of the Richmond Agitation Sedation Score (RASS) [19] and CAM-ICU [20] by well-trained nurses as recommended by the clinical practice guidelines for Pain, Agitation, and Delirium in ICU patients. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score $\geq$ -3 will be assessed for delirium with the use of the CAM-ICU scale **(supplementary material 2).**

The American guidelines on pain, agitation, and delirium management recommend [5,6]: 1/ the use of sedation scales to assess arousal level; 2/ if patients are assessable, the use of validated tools to assess for delirium, such as the Confusion Assessment Method-ICU (CAM-ICU) [20]. All four domains of the CAM-ICU, anchored on the presence of inattention, are evaluated in a focused patient assessment usually taking less than 2 min to complete. The CAM ICU scale is recognized as one of the leading assessment tools for delirium in the ICU. It has undergone extensive development, validation, and is routinely utilized [21,22].

Secondary endpoints

the full list of secondary endpoints is provided in **Box 2**.

Randomization and sequence generation

The randomisation will be performed using CleanWEB, a 24/7 online centralise procedure service running. 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

The number of experimental units per block will be kept confidential to avoid prediction of future patient's allocation. 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). Allocation concealment will be ensured, as CleanWeb services will not release the randomization code until the patient has been recruited into the trial. Patient allocation will only be disclosed after the enrolment and the dedicated statistician will be blinded to the arm's allocation until the end of analysis.

Follow-up

ICU stay

In both groups, patients will have a standardized management of analgesia, sedation, delirium, MV weaning and early mobilization according to current guidelines. This will ensure that the tested strategy is efficient by itself when applied along with other recommended clinical practices in ventilated patients, especially those known to have an impact on delirium occurrence. 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. Nurses in charge will have at their disposal a daily sheet including standard surveillance and clinical pathways to follow according to surveillance. Clinical pathways aim to plan, rationalize, and standardize multiprofessional management of patients with similar health problems based on recommendations to limit the variability of practices. Clinical pathways also ensure the traceability of these practices. Our clinical pathways were established according to currently available guidelines [5]. The daily sheets from D0 to D14 will be grouped in a booklet in A3 format to ensure better readability. An explicit training to use the booklet and the clinical pathways is planned before the start of the study (**supplementary materials 3 to 6**) and include:

1) Routine pain, agitation and delirium assessment will be performed every 12 hours (and more frequently as needed) using valid and reliable assessment tools, including the behavioural pain scale (BPS) [23], the Richmond Agitation Sedation Scale (RASS) [19] and the CAM-ICU [20], in accordance with guidelines [5,6].

2) Management of pain, agitation and delirium can be summarized as follows: Analgesia will be adapted to maintain BPS ≤ 4. Patients will be considered to be in significant pain if they have a BPS score of 6 or greater. Sedation will be adapted continuously to maintain a RASS score compatible with patient's management, i.e. from -1 to +1 (i.e., drowsy/alert to calm/restless) in general cases and from -5/-4 to -3 (i.e. deep sedation to moderate sedation) in case of severe acute respiratory distress syndrome (ARDS) or refractory intracranial hypertension. In case of RASS score ≥ -3 assess delirium every 12 hours using CAM-ICU and more often as needed. In case of significant pain (BPS ≥ 6), agitation (RASS ≥ +2) or delirium (CAM-ICU positive), the nurses will refer to specific clinical pathways including a physician alert process.

3) Clinical pathways to manage agitation will differ between groups since severe agitation with a RASS score ≥ +3 will require a temporary physical restraint (< 24 hours) in the restrictive use of PR group.

The PAD management strategies will be associated with other ICU interventions that are known to impact delirium occurrence or duration, i.e spontaneous awakening trial, spontaneous breathing trial and early mobilization protocols.

Follow-up consultation at D90

A consultation will be performed at D90 by a psychologist (or a trained investigator/study coordinator). This consultation will be carried out face-to-face or by teleconsultation. If the follow up is carried out by teleconsultation, an information note, specifying that no recording of the consultation will be made, will be sent to the patient. The non-objection of the patient will be sought and noted in the medical file. A core outcome set of measures will be assessed during the consultation, including cognitive capabilities, post-traumatic stress disorder, functional disability using appropriate scales (see Box 1 and figure 1).

STATISTICAL CONSIDERATIONS

Sample size calculation

In the literature, the number of delirium-free and coma-free days between D0 and D14 is estimated at 10.5 ± 3 days in the systematic PR group [24,25]. We therefore expect a 1-day reduction in delirium duration in the restrictive PR group with a number of delirium-free and coma-free days estimated at 11.5 days. We assumed a sample of 191 inclusions per arm to achieve 90% power to detect a difference of 1 day in the mean number of delirium-free and coma-free days over 14 days between the two groups at a 0.05 significance level. To allow the require power for the per-protocol analysis the sample size required is 422 (allowing for an estimated 9% loss to follow-up). Relying on the active participation of the 10 participating centres, we estimate that the inclusion time will be 38 months (assuming the number of inclusions at 1.1 patients per month per centre). To ensure the 422 planned inclusions and the 3-month follow-up of all included patients, a research duration of 41 months is expected. Participant recruitment started on January 25th, 2021.

Statistical analyses

The number of delirium-free and coma-free days between D0 and D14 will be compared between the two experimental groups, systematic use group vs. restrictive use group by a Student's test or a Wilcoxon Rank-Sum test if no normality of criteria. If the patient dies within 14 days, the number of non-surviving days will be considered days of coma. If the patient is discharged before D14, after extubation, the number of days remaining will be considered delirium-free and coma-free days. If the patient is discharged before D14, always in MV, the number of days remaining will be considered delirium days. The main analysis will be in intent to treat (ITT), that is, patients will be analysed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analysed in the arm of management received. For the analysis of patients who leave the service before D14, we will perform a sensitivity analysis, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14, by a linear regression with adjustment on these 3 continuous factors. 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. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of invasive MV. In case if significant interaction, a sub-group analysis will be performed.

Secondary analyses will be performed in ITT and then in Per-protocol. The continuous secondary criteria of duration and cumulative doses of sedative agents', analgesics and or antipsychotics between D0 and D14 will be compared between the two experimental groups, systematic use group vs. restrictive use group, by a Student test or a Wilcoxon Rank-Sum test. The categorical secondary criteria will be compared by a Chi-square test or an exact Fisher test if appropriate.

The significant level of all statistical analyses will be a two-sided 5% and the confidence interval at 95%. We will not perform adjustments for multiple outcomes in our 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 [26].

All statistical analyses will be performed using SAS software (SAS Institute Inc., Cary, NC) v. 9.4 or later, or R software (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/) v. 4.0 or later. All analyses will be conducted by a statistician according to a prespecified statistical analysis plan. A full statistical analysis plan has been written and is available in **supplementary material 7**. All analyses results will be reported according to the Consolidated Standards of Reporting Trials (STROBE) 2010 guidelines [27].

Data collection and management

Data collection will be done in electronic format using CleanWeb software. The software will fulfil the regulatory requirements and security norms. Data will be handled according to the French law. All original records (including consent forms, reports of suspected unexpected serious adverse reactions and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years.

We will collect data on primary and secondary endpoints, as well as potential risk factors of delirium (ICU medication, comorbidities, and complications) detailed in **table 1**.

The data of this study will be available upon reasonable request from the corresponding author. The data will not be publicly available due to privacy or ethical restrictions.

PATIENT AND PUBLIC INVOLVEMENT

Patients and public were not involved in any of the phases of this study. Results of the trial will be made available to all participants via ClinicalTrials.gov as well as by email notification.

TRIAL STATUS

Recruiting. The first inclusion occurred on the 21st of January 2021 and the recruiting period will last 39 months. On March 12th 2024, 422 patients have been included and follow-up is ongoing.

ETHICS AND DISSEMINATION

Legal obligations and approval

Sponsorship has been agreed by Assistance Publique—Hôpitaux de Paris (AP-HP, Clinical Research and Innovation Department) for this non-interventional human research study. AP-HP has obtained the favourable opinion of the independent ethics committee "Comité de Protection des Personnes (CPP) ILE DE FRANCE III – PARIS (CPP19.09.06.37521) for the study protocol (version R2D2−05.0; March 3, 2023). The trial will be carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Any substantial modification to the protocol must be sent to the sponsor for approval. Once approval has been received from the sponsor, it must also obtain approval from the CPP before the amendment can be implemented. The information sheet and the consent form can be revised, if necessary, particularly if there is a substantial amendment to the study or if adverse reactions occur. AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

Methods for obtaining information from research participants

In accordance with Article L.1122-1-1 of the French Public Health Code, no research mentioned in 3° of this article (like R2D2 protocol) can be carried out on a person without his/her free and informed non opposition, obtained in oral after the person has been given the information specified in Article L.1122-1 of said Code.

The trustworthy persons/relatives of eligible patients will be informed of the modalities of implementation of the study through an information note and a consent form (see **supplementary material 8**) and oral explanations given by the investigating physician or any qualified person. This information and consent forms will also be given to the patient concerned as soon as his neurological condition allows it.

Indeed, at the time of inclusion, the person participating in the research is often not in a state to give their consent; the inclusion in the R2D2 protocol is therefore done without prior agreement of the

patient. Inclusion in the R2D2 protocol is done as soon as the patient is consecutively hospitalized in ICU and requires IMV: it is therefore not always possible to obtain the consent of the person before his inclusion in the trial.

The protocol therefore provides that the consent of this person is not systematically sought at inclusion and that only the non-opposition of family members or the trusted person is sought, and the informant (investigator or collaborator) will have sufficient time (the first 3 days of the patient's resuscitation) to proceed with clear and informed information, imperatively before the patient's inclusion in the research.

The information will be given to the patient and his consent will be sought at the time when his neurological state allows it.

The information and the collection of the consent of the patient or trusted person/relative is collected by the principal investigator, or by a physician who represents him/her, or by a qualified person in the participating centre.

Thus, 2 types of information document are provided for:

- one for the trusted person/close relative if he/she is present at the time of inclusion when the patient is unable to be informed.

- one for the patient as soon as he/she is able to consent to the continuation of the research.

A copy of the information document is given to the person participating in the research. The information given to the subject will be recorded in his or her medical file. Subjects may exit the study at any time and for any reason.

DATA COLLECTION AND QUALITY CONTROL

The persons responsible for the quality control of clinical matters will take all necessary precautions to ensure the confidentiality of information relating to the study participants. These persons, as well as the investigators themselves, are bound by professional confidentiality. During or after the research, all data collected about the participants and sent to the sponsor by the investigators (or any other

specialised collaborators) will be anonymised. Under no circumstances should the names, addresses and other protector identifiers of the subjects involved be shown.

A data monitoring committee (DMC) has not been convened, on the grounds that the study is low risk. This has been approved by the Sponsor, Steering Committee, and the independent Ethical Board. The research data will be collected and monitored using an eCRF through CleanWEB Electronic Observation Book and will be centralised on a server hosted by the AP-HP Operations Department. This research is governed by the CNIL 'Reference Method for processing personal data for clinical studies' (MR-001, amended). AP-HP, the sponsor, has signed a declaration of compliance with this 'Reference Method'.

An independent Clinical Research Associate appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording, and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the Clinical Research and Innovation Department of AP-HP. The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits. These audits and inspections cannot be refused on the grounds of medical secrecy. An audit can be carried out at any time by independent individuals appointed by the sponsor. The aims of the audits are to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force. The persons who manage and monitor the study agree to comply with the sponsor's audit requirements. The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study. Sponsor is responsible for access to the study database.

SAFETY CONSIDERATIONS

The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.

TRIALS OVERSIGHT COMMITTEES

Two oversight committees have been established to oversee the conduct of this trial, the Steering Committee and Scientific Committee, the composition of each is listed at the end of this paper.

PUBLICATION PLAN

Scientific presentations and reports corresponding to the study will be written under the responsibility of the coordinating investigator of the study with the agreement of the principal investigators and the methodologist. The co-authors of the report and the publications will be the investigators and clinicians involved, on a pro rata basis of their contribution in the study, as well as the biostatistician and associated researchers. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the R2D2 investigators' in the final manuscript. Rules on publication will follow international recommendations.[28]

Author contributions The planning, study design and conception were primarily led by RS, CC, VG, and LB. Methodology, and the statistical analysis plan were chiefly orchestrated by CC, CR and RC. Data management was coordinated by VG and RB. Patient recruitment efforts were coordinated by RS, FS, JA, DC, AC, MD, JC, PJ, AMD, CB, and JFT. RS, CC, and LB wrote the manuscript. All authors contributed to the critical revision of the manuscript and gave final approval for its publication.

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Competing interest statement Romain Sonneville received grants from the French Ministry of Health and from LFB. Other authors declare no competing interests.

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PARIS, grant number PHRC-N 2017. The sponsor had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

FIGURE LEGEND

Figure 1. Flow diagram.

Mechanical ventilation, RASS Richmond Agitation Sedation Scale, CAM-ICU Confusion Assessment Method for the ICU, MMSE Mini Mental State Evaluation, FAB Frontal Assessment Battery, IES-R Impact of Events Scale-revised, IPREA Inconforts des Patients de REAnimation, GOS-E Glasgow Outcome Scale-Extended, FIM Functional Independence Measure, MRC Medical Research Council Scale.

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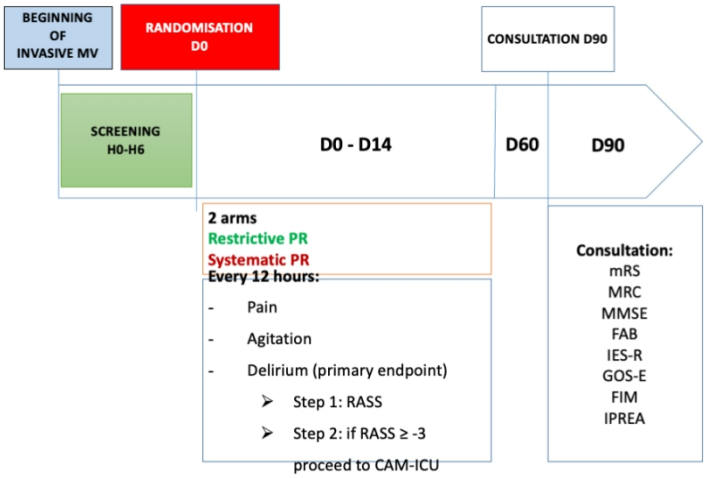

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Mechanical ventilation, RASS Richmond Agitation Sedation Scale, CAM-ICU Confusion Assessment Method for the ICU, MMSE Mini Mental State Evaluation, FAB Frontal Assessment Battery, IES-R Impact of Events Scale-revised, IPREA Inconforts des Patients de REAnimation, GOS-E Glasgow Outcome Scale-Extended, FIM Functional Independence Measure, MRC Medical Research Council Scale.

338x190mm (95 x 95 DPI)

Restrictive use of Restraints and Delirium Duration in ICU (R2D2-ICU): protocol for a multicenter parallel-group open label randomized controlled trial

SUPPLEMENTAL MATERIAL 1: SPIRIT CHECKLIST

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P4 P20
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	P20
Funding	4	Sources and types of financial, material, and other support	P24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1 P23
	5b	Name and contact information for the trial sponsor	P1 P24
	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	P23
	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)	P23
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	P6
	6b	Explanation for choice of comparators	P6 P10
Objectives	7	Specific objectives or hypotheses	P7 BOX1

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)	P9 P15
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	P13
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)	P10 BOX2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10 TABLE1
	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)	P10 SM3-SM6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P21
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P23 TABLE1 SM3-SM6
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	P14 BOX1
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)	TABLE1 FIGURE1
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	P17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P13
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	P15
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	P15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P15 P21
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P15
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	P21
	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	P21
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	P21
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	P17 SM7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P17 SM7
	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)	P17 SM7
Methods: Monitoring			

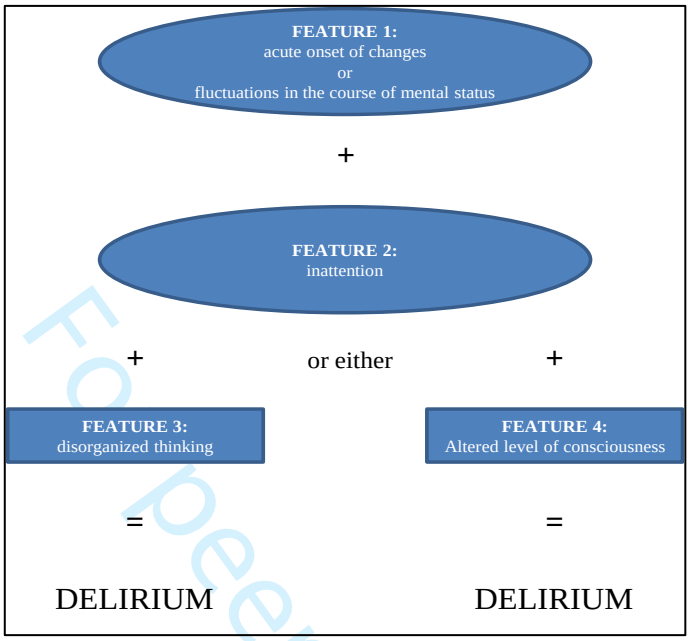
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NOT APPLICABLE
	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	NOT APPLICABLE
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	P21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NOT APPLICABLE
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P20
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)	P20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P9 TABLE1 P19 P20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NOT APPLICABLE
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	P20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P24
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	P20
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	NOT APPLICABLE

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	P20
	31b	Authorship eligibility guidelines and any intended use of professional writers	P20
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	P20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NOT PROVIDE
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	NOT APPLICABLE

SUPPLEMENTAL MATERIAL 2: DELIRIUM ASSESSEMENT

CAM = Confusion Assessment Method

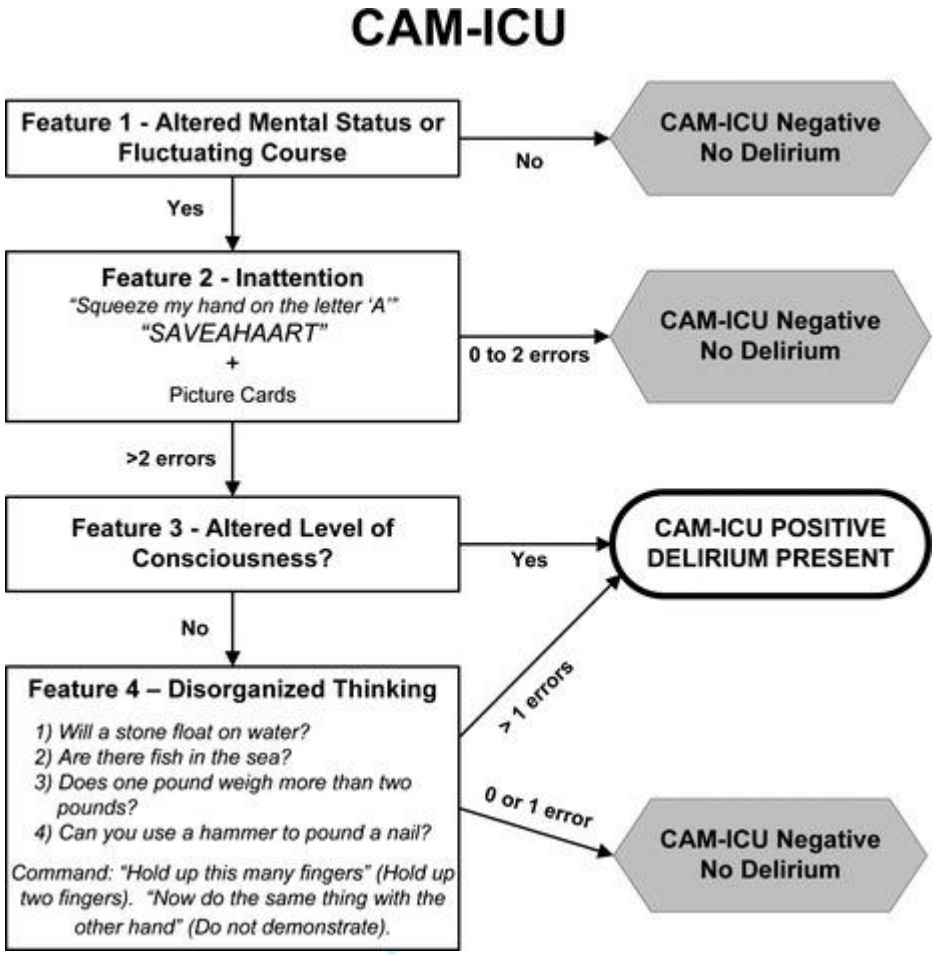
The Confusion Assessment Method (CAM) was created in 1990 by Dr. Sharon Inouye, and it was intended to be a bedside assessment tool usable by non-psychiatrists to assess for delirium [38]. Delirium is defined in terms of four diagnostic features, and is deemed positive when Feature 1 and Feature 2 and either Feature 3 or 4 are present (see CAM and CAM-ICU schematics).



CAM Confusion Assessement Method		
	The diagnosis of delirium by CAM requires the presence of **BOTH** features ***A*** and ***B***	
	A = acute onset and fluctuating course	Is there evidence of an acute change in mental status from patient baseline? Does the abnormal behavior: ➢ come and go? ➢ fluctuate during the day? ➢ increase/decrease in severity?
	B = Inattention	Does the patient: ➢ have difficulty focusing attention? ➢ become easily distracted? ➢ have difficulty keeping track of what is said?
	AND the presence of **EITHER** feature **C** or **D**	
	C = Disorganized thinking	Is the patient's thinking ➢ disorganized ➢ incoherent For example does the patient have ➢ rambling speech/irrelevant conversation? ➢ unpredictable switching of subjects? ➢ unclear or illogical flow of ideas?
	D = Altered level of consciousness	Overall, what is the patient's level of consciousness: ➢ alert (normal) ➢ vigilant (hyper-alert) ➢ lethargic (drowsy but easily roused) ➢ stuporous (difficult to rouse) ➢ comatose (unrousable)

The Confusion Assesement Method for the Intensive Care Unit (CAM-ICU)

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course A. Is there evidence of an acute change in mental status from baseline? **B.** Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidence by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Coam Glasgow Scale?	☐	☐
II. Inattention Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answerson either the visual or auditory components of the Attention Screening Examination (ASE)	☐	☐
III. Disorganized thinking Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stonefloat on water 2. Are there fish in the sea 3. Does 1 pound weigh more that 2 pounds 4. Can you use a hammer to pound a nail Commands 1. Are you having unclear thinking? 2. Hold up this many fingers(examiner holds 2 fingers in front of the patient) 3. Now do the same thing with the other hand (withoutholding the 2 fingers in front of the patient) (If the patient is already extubated from the ventilator, determine wether the patient's thinking is disorganized or incoherent, sucha s rambling or irrelevant conversation, unclear or illogical flow or ideas, or unpredictable switching from subject to subject)	☐	☐
IV. Altered level of consciousness Is the patients's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environement and interacts appropriately Vigilant: hyperalert Lethargic drowsy but easily aroused, unaware of some elements in the environement or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unware of some or all elements, in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapes back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding	☐	☐
Overall CAM-ICU Assessment (Features I and II and either feature III or IV): YES ☐ NO ☐		



The CAM-ICU is an adaptation of the CAM tool for use in ICU patients (e.g., critically ill patients on or off the ventilator) using nonverbal, objective tests derived through a comprehensive literature review and consulation with numerous delirium experts. (1). The CAM-ICU underwent extensive validation in the ICU setting and is, therefore, one of the delirium scores recommended by international guidelines (2). The Richmond Agitation Sedation Scale (RASS) is a component of the CAM-ICU (Feature 4: Altered Level of Consciousness).

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SUPPLEMENTAL MATERIAL 3: DAILY CRITICAL CARE MANAGEMENT OF SYSTEMATIC PHYSICAL RESTRAINT

GROUP
SYSTEMATIC PHYSICAL RESTRAINT

DATE
From D0 to D14 __ __/__ __/____

SCHEDULE (X = mandatory; x = if needed)	AM					PM											AM						
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
PAIN/SEDATION-AGITATION/DELIRIUM ASSESSEMENTS																								
I : Assess pain using BPS: TARGET ≤ 4 Refer to the specific clinical pathway on the back of the sheet if BPS > 4.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
II : Assess agitation/sedation using RASS : TARGET -1/0/+1 (-4/-5 in case of ARDS or ICH) Refer to the specific clinical pathway on the back of the sheet if RASS ≥ +3. **Mention physical restraint session |----|**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
III : Assess delirium only if RASS ≥ - 3 using CAM-ICU **Refer to the specific clinical pathway on the back of the sheet** criteria I +II and criteria III and /or IV present - Criteria I present (Yes/No) - Criteria II present (Yes/No) - Criteria III present (Yes/No) - Criteria IVpresent (Yes/No)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY SCREEN																								
I : SAT safety screen Follow and complete the clinical pathway on the back sheet. If appropriate do SAT and go to SBT. Mention both sedatives STOPS (SAT) and RESTARTS (R) times.	ONCE A DAY BETWEEN 8AM AND NOON																							
II : SBT safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do SBT. Mention both SBT, EXTUBATION (E), and REINTUBATION (R).	ONCE A DAY BETWEEN 8AM AND NOON																							
III : EM safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do EM according to patients'status Mention both (MAP, MAA, PV, BL, MFP, MFA, walk)	ONCE A DAY BETWEEN 8AM AND NOON																							

BPS = Behavioral pain scale; RASS = Richmond Agitation-Sedation Scale; SAT= spontaneous awakening trial; SBT = spontaneous breathing trial; EM = early mobilization

SUPPLEMENTAL MATERIAL 4: CLINICAL PATHWAYS ACCORDING TO BPS, RASS AND CAM-ICU ASSESSMENTS FOR THE SYSTEMATIC PHYSICAL RESTRAINT GROUP

Clinical pathways according to BPS, RASS, and CAM-ICU assessments

SIGNIFICANT PAIN: BPS ≥ 6

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of pain**

Check for a serious painful event (myocardial infarction, thromboembolic event, ileus, peritonitis)

2) **Choose the appropriate analgesic**

a. Use the WHO analgesic scale to treat a nociceptive pain.
   First WHO level: acetaminophen and/or nefopam
   Second WHO level: dextropropoxyfen or tramadol or nalbuphin.
   Third WHO level: morphine or fentanyl or patient-controlled analgesia.
b. Use a spasmolytic intestinal drug to treat an intestinal spasm.
c. Use centrally acting muscle relaxants to treat a muscle contracture.
d. d. Use anti-inflammatory nonsteroid drugs (AINS) to treat an inflammatory pain if first and second WHO level analgesics are inefficient.

SIGNIFICANT AGITATION: RASS ≥ +2

REFER TO THE PHYSICIAN IN CHARGE

1) **Physical restraint if RASS ≥ +3**
2) **Diagnose the source of agitation***
3) **Choose the appropriate drug**

a. Is the patient in pain? Cf. supra
b. Is the patient talking about anxiety? Consider use of benzodiazepine.
c. Is the patient delirious? Cf. infra.
d. Consider withdrawal syndrome if patient is a psychoactive and/or a third WHO level drug user or received continuous sedation in the last 48 hrs: test reintroduction of the drug, consider clonidine to withdraw previous treatment

REASSESSEMENT WITHIN 4 HOURS

DELIRIUM = CAM-ICI POSITIF

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of delirium***
2) **Choose the appropriate drug**

a. Use a neuroleptic in case of agitation (RASS ≥ +2)
   -Haldol® if the patient is confused or describing hallucinations
   -Nozinan® in case of predominant anxiety or sutained RASS ≥ 3
b. Use dexmedetomidine idf neuroleptics are inefficient or proscribed

REASSESSEMENT WITHIN 6 HOURS

*Serious painful event, brain injury, fever or sepsis), hydroelectrolytic disorders, acute urinary retention, fecal impaction, analgesic-associated

SUPPLEMENTAL MATERIAL 5: DAILY CRITICAL CARE MANAGEMENT OF SYSTEMATIC PHYSICAL RESTRAINT

GROUP
RESTRICTIVE PHYSICAL RESTRAINT

DATE
From D0 to D14 __ __/__ __/____

SCHEDULE (X = mandatory; x = if needed)	AM					PM											AM						
	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7
PAIN/SEDATION-AGITATION/DELIRIUM ASSESSEMENTS																								
I : Assess pain using BPS: TARGET ≤ 4 Refer to the specific clinical pathway on the back of the sheet if BPS > 4.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
II : Assess agitation/sedation using RASS : TARGET -1/0/+1 (-4/-5 in case of ARDS or ICH) Refer to the specific clinical pathway on the back of the sheet if RASS ≥ +3. **Mention physical restraint session |----|**	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
III : Assess delirium only if RASS ≥ - 3 using CAM-ICU **Refer to the specific clinical pathway on the back of the sheet** criteria I +II and criteria III and /or IV present - Criteria I present (Yes/No) - Criteria II present (Yes/No) - Criteria III present (Yes/No) - Criteria IVpresent (Yes/No)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
SAFETY SCREEN																								
I : SAT safety screen Follow and complete the clinical pathway on the back sheet. If appropriate do SAT and go to SBT. Mention both sedatives STOPS (SAT) and RESTARTS (R) times.	ONCE A DAY BETWEEN 8AM AND NOON																							
II : SBT safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do SBT. Mention both SBT, EXTUBATION (E), and REINTUBATION (R).	ONCE A DAY BETWEEN 8AM AND NOON																							
III : EM safety screen if appropriate Follow and complete the clinical pathway on the back sheet. If appropriate do EM according to patients'status Mention both (MAP, MAA, PV, BL, MFP, MFA, walk)	ONCE A DAY BETWEEN 8AM AND NOON																							

BPS = Behavioral pain scale; RASS = Richmond Agitation-Sedation Scale; SAT= spontaneous awakening trial; SBT = spontaneous breathing trial; EM = early mobilization

SUPPLEMENTAL MATERIAL 6: CLINICAL PATHWAYS ACCORDING TO BPS, RASS AND CAM-ICU ASSESSMENTS FOR THE RESTRICTIVE PHYSICAL RESTRAINT GROUP

Clinical pathways according to BPS, RASS, and CAM-ICU assessments

SIGNIFICANT PAIN: BPS ≥ 6

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of pain**

Check for a serious painful event (myocardial infarction, thromboembolic event, ileus, peritonitis)

2) **Choose the appropriate analgesic**

a. Use the WHO analgesic scale to treat a nociceptive pain.
First WHO level: acetaminophen and/or nefopam
Second WHO level: dextropropoxyfen or tramadol or nalbuphin.
Third WHO level: morphine or fentanyl or patient-controlled analgesia.

b. Use a spasmolytic intestinal drug to treat an intestinal spasm.

c. Use centrally acting muscle relaxants to treat a muscle contracture.

d. d. Use anti-inflammatory nonsteroid drugs (AINS) to treat an inflammatory pain if first and second WHO level analgesics are inefficient.

SIGNIFICANT AGITATION: RASS ≥ +2

REFER TO THE PHYSICIAN IN CHARGE

1) **Physical restraint if RASS ≥ +3**
2) **Diagnose the source of agitation***
3) **Choose the appropriate drug**

a. Is the patient in pain? Cf. supra

b. Is the patient talking about anxiety? Consider use of benzodiazepine.

c. Is the patient delirious? Cf. infra.

d. Consider withdrawal syndrome if patient is a psychoactive and/or a third WHO level drug user or received continuous sedation in the last 48 hrs: test reintroduction of the drug, consider clonidine to withdraw previous treatment

REASSESSEMENT WITHIN 4 HOURS

DELIRIUM = CAM-ICI POSITIF

REFER TO THE PHYSICIAN IN CHARGE

1) **Diagnose the source of delirium***
2) **Choose the appropriate drug**

a. Use a neuroleptic in case of agitation (RASS ≥ +2)
-Haldol® if the patient is confused or describing hallucinations
-Nozinan® in case of predominant anxiety or sutained RASS ≥ 3

b. Use dexmedetomidine idf neuroleptics are inefficient or proscribed

REASSESSEMENT WITHIN 6 HOURS

*Serious painful event, brain injury, fever or sepsis), hydroelectrolytic disorders, acute urinary retention, fecal impaction, analgesic-associated

SUPPLEMENTAL MATERIAL 7: STATISTICAL ANALYSIS PLAN FOR A MULTICENTER PARALLEL-GROUP OPEN LABEL RANDOMIZED CONTROLLED TRIAL

(VERSION DECEMBER 12 2023)

Table

1 ENDPOINTS

Endpoints will be compared between randomization groups (restrictive use of PR vs. systematic use of PR).

1.1. Primary endpoint

It will be the number of delirium-free or coma-free days, defined as the number of days in the first 14 days after randomization during which the patient was alive without delirium or not in coma from any cause. This endpoint will be assessed twice a day by the French validated translation of the Richmond Agitation Sedation Score (RASS) and CAM-ICU by well-trained nurses. Patients with a RASS of -5 or -4 will be considered comatose. Patients with a RASS score > or = -3 will be assessed for delirium with the use of the CAM-ICU scale.

1.2. Secondary endpoints

1.2.1 Delirium duration until ICU discharge

This criterion is defined by the number of days on delirium until ICU discharge, the proportion of positive CAM-ICU until ICU discharge.

1.2.2 Incidence of delirium between D0 and D14

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 and D14.

1.2.3 Incidence of delirium until ICU discharge

This criterion is defined by the rate of patients with at least one delirium day (positive CAM-ICU) between D0 until ICU discharge.

1.2.4 Agitation duration between D0 and D14

This criterion is defined by the number of days alive with agitation (RASS ≥ 2) between D0-D14.

1.2.5 Exposure to analgesic (opioids) between D0 and D14

This criterion is defined by the total cumulative dose of opiod analgesics (and subclass of opioids) between D0 and D14.

1.2.6 Exposure to propofol between D0 and D14

This criterion is defined by the total cumulative dose of propofol between D0 and D14.

1.2.7 Exposure to benzodiazepines between D0 and D14

This criterion is defined by the total cumulative dose of benzodiazepines as anxiolytic between D0 and D14.

1.2.8 Exposure to antipsychotic agents between D0 and D14

This criterion is defined by the total cumulative dose of antipsychotics agents (Haloperidol, Levomepromazine and Cyamemazine) between D0 and D14.

1.2.9 Exposure to dexmetomidine between D0 and D14

This criterion is defined by the total cumulative dose of dexemtomidine between D0 and D14

1.2.10 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

This criterion is defined by the total number of hours without mechanical ventilation between D0 and D14.

1.2.11 Patient mobility according to the visual global mobilisation score between D0 and D14

This criterion is defined by the Median of Mobilisation capacity and rate of patients > 2 on a visual scale ranging from 0 (no mobilisation) to 4 (ambulation) between D0- D14.

1.2.12 Incidence of self-extubation and device removal between D0 and D14

This criterion is defined by the rate of patients with at least one self-extubation or any device removal (Central catheter, arterial catheter or urinary catheter) between D0 and D14.

1.2.13 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

This criterion is defined by the rate of patients with pressor ulcer on the wrists and with other bedsores and their severity according to the National Pressure Ulcer Advisory Panel between D0-D14 (at least one ulcer of grade III or IV per patient).

1.2.14 ICU and hospital lengths of stay

This criterion is defined by the number of hospitalization day.

1.2.15 In-ICU and in-hospital mortality

This criterion is defined by the mortality rate on ICU stay and during hospitalization.

1.2.16 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

This criterion is defined by:

- The rate of patients with at D90 an altered cognitive capability defined as a MMSE (Mini Mental State Examination) ≤ 24 points
- The rate of patients with a frontal syndrome defined as a FAB (Frontal Assessment Battery at Bedside) < 15 points
- The rate of patients with a possible diagnosis of Post-Traumatic Stress Disorder (PTSD) defined as a R-IES (Revised-Impact of events scale) ≥ 33 points
- The rate of patients with a functional disability defined as a GOS-E (Glasgow Outcome Scale – Extended) ≤ 6 points
- The rate of patients with functional independence, evaluated by the FIM (Functional Independence Measurement)

2 GENERAL CONSIDERATIONS

2.1. Flowchart

A flowchart following *Consolidated Standards of Reporting Trials (CONSORT)* standards, describing patients flow throughout the study, included and randomized, will be provided. The flowchart will specify the number of patients in each arm and describe loss of patients during the study.

2.2. Level of statistical significance

In this study, the statistical level of significance (Type I error) will be fixed at 5%.

2.3. First day of patient- follow-up (D0)

The first day of patient follow-up (D0) is the day of randomization. This day is the reference day which will be used as the initial date in the calculation of all delays.

3 STATISTICAL ANALYSIS

3.1. Descriptive analysis

The variables that will be described are as follows:

- Comorbidities/Demographic data of the included population and at ICU admission

- Treatments administred at ICU admission (Ketamine, Etomidate, Propofol and others)
- Clinical and biological data at ICU admission and from D1 to D14
- Clinical scores at ICU admission and from D1 to D14
- End-of-study data/Discharge assessment
- Clinical scores at D90

The dedicated score to assess the delirium-free and coma-free days will be described per day – morning and evening assessment. A time plot will be provided to allow a graphical description of the quality assessment between D0 and D14. Melatonin exposure will be described per day and on total, with normalization on number of days on ICU to allow patients discharged before D14 to be taken into account.

All qualitative variables will be described by their number and corresponding frequency. Quantitative variables will be described by their min and max, mean and standard deviation, median, Q1 and Q3. For each variable, the number and frequency of missing data will be reported. The description will be made for all patients and then according to the randomisation group (systematic PR vs. restrictive PR). The total number of patients and in each group will be specified. Melatonin exposure description will be also made according to the use of different devices in the medical room (i.e. earplugs, masks, natural light).

Results of descriptive analysis will be presented in tables as follows:

	Total population (N=)	Systematic PR (N=)	Restrictive PR (N=)
Quantitative variable			
	Range	Range	Range
	Median [IQR]	Median [IQR]	Median [IQR]
	Mean (SD)	Mean (SD)	Mean (SD)
	NA (n (%))	NA (n (%))	NA (n (%))
Qualitative variable			
« First modality »	% (n/N)	% (n/N)	% (n/N)
« Second modality »	% (n/N)	% (n/N)	% (n/N)
Missing	% (n/N)	% (n/N)	% (n/N)

3.2. Analysis of the primary endpoint

Analysis set

The main analysis will be in intent to treat (ITT), that is, patients will be analyzed in the initially allocated management arm and not according to the actual management received. Then the main analysis will be replicated in per-protocol (if any), each patient will be analyzed in the arm of management actually received.

Descriptive statistics and graphical representation

Results of CAM-ICU (Positive/Negative/Not done) will be described each day and for each evaluation, with sample size and proportion of patients in each modality, from D0 to D14, on total population and according to the randomisation group.

We will construct a variable summarizing CAM-ICU results each day (Morning CAM-ICU positive and evening CAM-ICU negative/Morning CAM-ICU negative and evening CAM-ICU positive/Both morning and evening CAM-ICU positives/Both morning and evening CAM-ICU negatives) from D0 to D14. This variable will be described with sample size and proportion of patient in each modality, from D0 to D14, on total population and according to the randomisation group.

The number of patients without coma and delirium will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The number of delirium-free and coma-free days will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made for all patients and then according to the randomisation group.

Statistical methodology

A variable corresponding to the number of delirium-free and coma-free days between D0 and D14 (primary endpoint) will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where all CAM-ICU evaluations (morning, evening or supplementary CAM-ICU evaluations) are negative. Each day, from D0 to D14, primary endpoint for ICU discharged patients will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days will be considered days of coma.

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all RASS or CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by days with coma.
- If there are non-missing data before and after the missing data and data before missing data show RASS ≥ -3 (patient not considered comatose), missing result will be imputed by days without coma.
- It will be considered that a delirium day cannot be a coma day and vice versa, meaning that in case of days with RASS ≤ -4 (patient considered comatose), and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value and in case of days with positive CAM-ICU and missing RASS, RASS results are imputed by no coma days.
- In case of missing data until D14, a last value carried forward imputation method will be performed, for both RASS and CAM-ICU

The number of coma or delirium free days between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon text as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3. Analyses of secondary endpoints

3.3.1 Delirium duration until ICU discharge

Analysis set

This analysis will be performed on the sub-population of patients having at least one day of delirium between D0 and D14.

Descriptive statistics and graphical representation

The number of days with delirium (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The proportion of positive CAM-ICU until ICU discharge will be described using frequencies, on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

The number of CAM-ICU performed until ICU discharge will be constructed for each patient. This variable will be described using min and max, mean and standard deviation, median, Q1 and Q3. The description will be made on the total sub-population of patients having at least one day of delirium between D0 and D14 and according to the randomisation group on this sub-population.

Statistical methodology

The number of days with delirium will be constructed. It will correspond for each patient to the total amount of days from D0 to D14 where at least one of the morning, evening or supplementary CAM-ICU evaluations is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.

- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the "Not done" value
- In case of missing data until D14, a last value carried forward imputation method will be performed

Number of days with delirium between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

The proportion of positive CAM-ICU until ICU discharge will be compared between randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test. Proportions of positive CAM-ICU will be presented with 95% confidence intervals according to the randomisation group.

The number of CAM-ICU performed until ICU discharge will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.2 Incidence of delirium between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with delirium (constructed variable, see below) will be described each day, between D0 and D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

Patients with delirium between D0 and D14 are defined as patients experiencing delirium at least one day from D0 to D14, a delirium day being a day with at least one of the morning, evening or supplementary CAM-ICU evaluations that is positive. Each day, from D0 to D14, this endpoint will be imputed by:

- No coma and delirium day if the patient is discharged before D14 and after extubation
- Delirium day if the patient is discharged before D14, always in MV

For patients dying within 14 days, the number of non-surviving days are not considered as delirium days (coma days only).

In case of days with partial missing data for CAM-ICU result (meaning at least one of the morning, evening or supplemental CAM-ICU evaluations are missing), we will impute the missing result by the non-missing result of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with patients having days with missing data for all CAM-ICU results of the day (both morning, evening and supplemental CAM-ICU evaluations), we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show positive CAM-ICU, missing result will be imputed by positive CAM-ICU.
- If there are non-missing data before and after the missing data and data before missing data show negative CAM-ICU, missing result will be imputed by negative CAM-ICU.
- It will be considered that a coma day cannot be a delirium day, meaning that in case of days with RASS ≤ -4 (patient considered comatose) and missing CAM-ICU, CAM-ICU results are imputed by the “Not done” value.
- In case of missing data until D14, a last value carried forward imputation method will be performed

Rate of patients with delirium between D0 and D14 will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients with delirium between D0 and D14 with 95% confidence intervals and according to the randomisation group.

3.3.3 Agitation duration between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The number of days with agitation (constructed variable, see below) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

The number of days with agitation between D0 and D14 will be a constructed variable, indicating for each patient the total amount of days where the patient is alive with RASS ≥ 2. Imputation methods for this endpoint are as follows:

- If the patient is discharged before D14, after extubation, the remaining days are considered no agitation days.
- If the patient is discharged before D14, always in MV, the remaining days are considered agitation days.
- If the patient dies within 14 days, the number of non-surviving days are considered as no agitation days.

In case of partial missing RASS evaluation (i.e. at least one of the morning, evening or supplemental RASS evaluation is not missing), we will impute the missing RASS evaluation by the non-missing evaluation of the corresponding day. In case of different non missing results in the same day, the positive result is retained. To handle with days with total missing RASS evaluation, we will impute as follow:

- If there are non-missing data before and after the missing data and both data before and after missing data show RASS ≤ -4 (patient considered comatose), missing result will be imputed by coma days (i.e. RASS ≤ -4).
- In case of missing data until D14 for RASS score, a last value carried forward imputation method will be performed

The number of days with agitation between D0 and D14 will be compared between randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-values of the test.

3.3.4 Exposure to analgesic (opioids) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Doses of analgesic (opioids) will be described each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Total cumulative dose of analgesic (opioids) from D0 to D14 will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. Total cumulative doses of analgesic (opioids) between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.5 Exposure to propofol between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative doses of propofol from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of propofol between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.6 Exposure to benzodiazepines between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

Total cumulative dose of benzodiazepines from D0 to D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of benzodiazepines between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.7 Exposure to antipsychotic agents between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose from D0 to D14 for each antipsychotic agent (i.e. Haloperidol, Levomepromazine and Cyamemazine) will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The same description will be made for total cumulative dose of all antipsychotic agent.

Statistical methodology

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of antipsychotic agents between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.8 Exposure to dexmedetomidine between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

Total cumulative dose of dexmedetomidine will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical method

There will be no methods for replacing missing data. To allow discharge before D14 to be taken into account, the total cumulative dose will be normalized by the number of days in intensive care between D0 and D14.

Total cumulative doses of dexmedetomidine between D0 and D14 will be compared according to the randomisation group using Sudent's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.9 Exposure to Invasive mechanical ventilation (IMV) between D0 and D14

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The number of patients exposed to IMV will be described each day, from D0 to D14, using frequencies. The description will be made for the total population and according to the randomisation group. The same description will be made for the number of patients exposed to IMV between D0 and D14.

The total amount of hours under IMV between D0 and D14 will be described using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For invasive mechanical ventilation exposure, it will be considered that:

- If the patient is discharged before D14, after extubation, the remaining days are not considered as days with exposure to invasive mechanical ventilation
- If the patient is discharged before D14, always in MV, the remaining days are considered as days with MV
- If the patient is discharged before D14, not in MV, the remaining days are considered as days without MV
- If the patient dies within 14 days, the remaining days are considered as days with MV

Exposure to IMV will be compared according to the randomisation group using student's t-test or Wilcoxon as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.10 Patient mobility according to the visual global mobilisation score between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The visual global mobilisation score will be descripted each day, from D0 to D14, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The visual global mobilisation score will be also descripted for the total D0-D14 period, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The rate of patients with global mobilisation score > 2 will be described each day, from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

Boxplots of the visual global mobilisation score from D0 to D14 will be realized to allow graphical representation of patient mobility.

Statistical methodology

There will be no methods for replacing missing data. The median of the visual mobilisation score on the D0-D14 period will be firstly normalized by the number of days under ICU hospitalization, to allow discharge from ICU or death before D14 to be taken into account. Normalized visual mobilisation score on the D0-D14 period will be compared between randomisation group using Wilcoxon test. Results will be presented using median and p-value of the test.

3.3.11 Incidence of self-extubation and device removal between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patient experiencing self-extubation will be described for each device (self-extubation, removal of central catheter, arterial catheter or urinary catheter), each day for D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group.

The same description will be realized for self-extubation or any device removal and for any device removal only.

Statistical methodology

The proportion of patients with self-extubation or any device removal will be compared between randomisation groups using chi-squared or Fisher test as appropriate. The same comparison between randomisation groups will be made for patients experiencing self-extubation only and for patients experiencing any device removal only. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.12 Skin lesions (wrist, heel and sacrum) occurrence between D0 and D14

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The proportion of patients with skin lesions will be described for each skin lesion (wrist, heel, sacrum, other), each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

The proportion of patients with at least one of the four types of skin lesions (wrist, heel, sacrum, other) will be described, each day from D0 to D14, using frequencies. This description will be made on the total population and according to the randomisation group. The same description will be made for the total D0-D14 period.

Statistical methodology

The proportion of patients with wrist lesions, the proportion of patients with heel lesions, the proportion of patients with sacrum lesions, and the proportion of patients with other skin lesions between D0 and D14 and according to the randomisation group will be analysed individually using chi-squared or Fisher test as appropriate. Results will be presented using p-value of the tests as well as proportion of patients with each lesion with their 95% interval confidence and according to the randomisation group.

The same analysis will be realized for patients having at least one of the four types of skin lesion (wrist, heel, sacrum, other) between D0 and D14 using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test, as well as proportion of patients for each modality with 95% confidence intervals and according to the randomisation group.

3.3.13 ICU and hospital lengths of stay

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The ICU length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

The hospital length of stay will be described, using min and max, mean and standard deviation, median, Q1 and Q3. This description will be made on the total population and according to the randomisation group.

Statistical methodology

For patients dying within 14 days, it will be considered that they stayed in ICU and hospital from ICU admission to date of death and from hospital admission to date of death respectively. In case of missing date for ICU discharge or hospital discharge outside patients who died within 14 days, the date of discharge from ICU/hospital will be imputed by the date of the patient's last news.

ICU length of stay and hospital length of stay will be analysed between according to randomisation group using Student's t-test or Wilcoxon test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

3.3.14 In-ICU and in-hospital mortality

Analysis set

This analysis will be performed on the total population

Descriptive statistics and graphical representation

The proportion of dead patients will be described each day, from D0 to D14, using frequencies, on the total population and according to the randomisation group.

Statistical methodology

To allow lost-to-follow up patients to be taken into account, a Kaplan-Meier model will be realized, the event of interest being in-ICU death or in-hospital death. We will perform a log rank

test to compare survival distributions according to the randomisation group. Results will be presented using p value of the log rank test, as well as proportion of death at day 90 between randomisation groups with their 95% interval confidence and according to the randomisation group.

3.3.15 Global assessment of motor and cognitive functions and post-traumatic stress disorder (PTSD) at D90

Analysis set

This analysis will be performed on the total population.

Descriptive statistics and graphical representation

The rate of patients with altered cognitive capabilities at D90, the rate of patients with a frontal syndrome at D90, the rate of patients with a possible diagnosis of PTSD, the rate of patients with a functional disability at D90 and the rate of patients with a functional independence at D90 will be described using frequencies. These descriptions will be made on the total population and according to the randomisation group.

Statistical methodology

There will be no imputation for missing data. Each individual endpoint will be compared according to the randomisation group using chi-squared test or Fisher test as appropriate. Results will be presented using p-value of the test as well as proportion of patients with altered cognitive capabilities at D90, proportion of patients with a frontal syndrome at D90, proportion of patients with a possible diagnosis of PTSD, proportion of patients with a functional at D90 and proportion of patients with a functional independence at D90. Each proportion will be provided with their 95% interval confidence and according to the randomisation group.

3.3.16 Center effect, age group effect and presence of coma at beginning of IMV effect

The center effect will be assessed by testing interaction between trial arm and the center in a linear regression modelling the number of delirium-free and coma-free days between D0 and D14. We will perform the same analysis to test the effect of age group (<65 or ≥65 years) and the presence of coma at the beginning of IMV. Results will be presented using coefficients of the linear regression with 95% confidence intervals as well as p-value of the tests. In case if significant interaction, a sub-group analysis will be performed.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2.

3.4. Sensitivity analysis

3.4.1 Number of days lived without coma and without delirium for patients leaving ICU before D14

This analysis will consist of a multivariate linear regression predicting the number of days lived without coma and without delirium in the sub-population of patients leaving ICU before D14, taking into account the MV duration of patients between D0 and D14, the sedation time of patient between D0 and D14 and the duration during which the patient is not adapted to a resuscitation output according to the criteria predefined between D0 and D14.

Missing values for days lived without coma and delirium will be imputed using same methodologies as described in §3.2. Missing values for MV exposure will be imputed using same methodologies as described in §3.3.9. There will be no imputation for sedation time.

3.4.2 Physical restraint exposure

A sensitivity analysis will be performed on primary endpoint for patients whose exposure to either restrictive or systematic RA has been fully respected over the 14 days according to the predefined rules. In addition, an analysis will be carried out on patients who have had no change in their exposure to RA during the 14 days or until discharge from intensive care after extubation. Sedative exposure at intubation at D0

Sensitivity analysis for the primary endpoint will be performed on the sub-population of patients exposed to sedative agents at intubation at D0.

3.5. Subgroup analysis

3.5.1 Center effect, age group effect and presence of coma at beginning of IMV effect

In case of significant interaction for analyses described in §3.3.16, a sub-group analysis will be performed for the prediction of number of delirium-free and coma-free days between D0 and D14. An ANOVA will be used for comparison of number of delirium-free and coma-free days from D0 to D14 between centres. We will use Student's t-test test or Wilcoxon test as appropriate to compare number of delirium-free and coma-free days from D0 to D14 between age groups and according to presence of coma at beginning of IMV. Results will be presented using mean or median as appropriate and p-values of the test.

3.5.2 Covid patients

A subgroup analysis will be performed on patients exposed to COVID for the comparison of number of delirium-free and coma-free days between D0 and D14 and according to COVID exposure. We will use Sudent's t-test or Fisher test as appropriate. Results will be presented using mean or median as appropriate and p-value of the test.

4 SOFTWARE

Statistical analyses will be made using R v. 4.2.1 or later (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/), or SAS Version 9.4 or later (SAS Institute Inc., Cary,NC).25/03/2024 12:30:00