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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P6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 TABL E1
	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 TABL E1 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)	TABL E1 FIGU RE1
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			

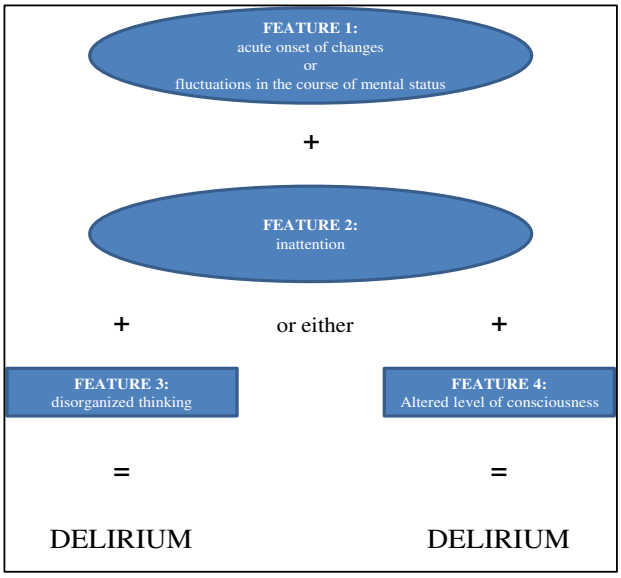
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, 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

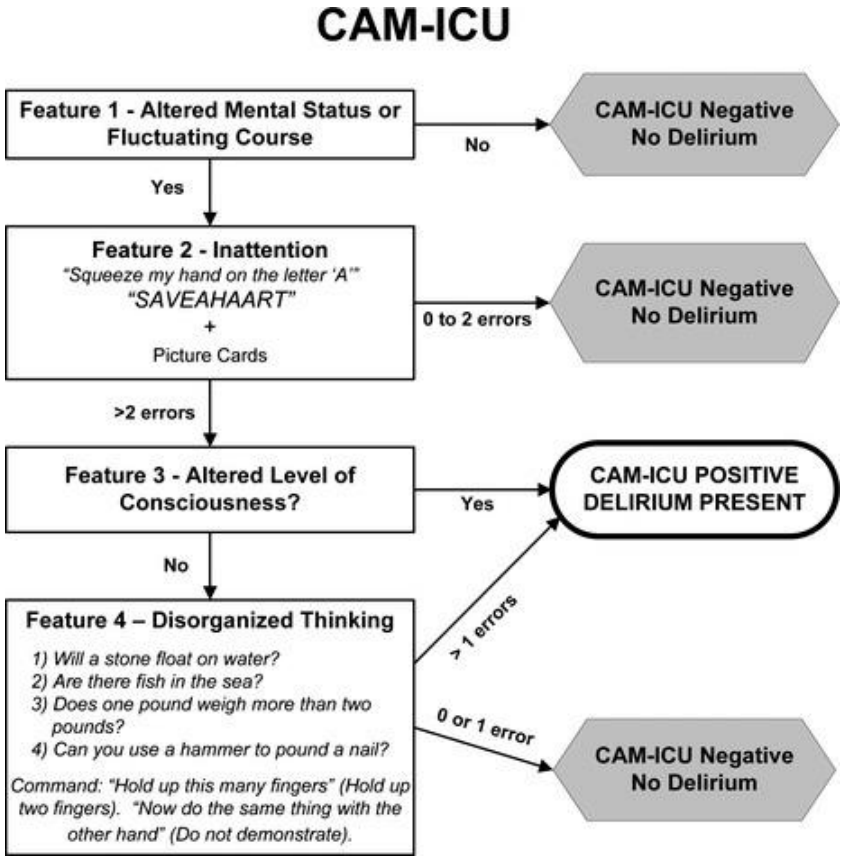
The Confusion Assessment Method (CAM) was created in 1990 by Dr. Sharon Inouye, and it was intended to be a bedside assessment tool usable by non-psychiatrists to assess for delirium [38]. Delirium is defined in terms of four diagnostic features, and is deemed positive when Feature 1 and Feature 2 and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

Sonneville R, *et al. BMJ Open* 2024; 14:e083414. doi: 10.1136/bmjopen-2023-083414

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

Sonneville R, *et al. BMJ Open* 2024; 14:e083414. doi: 10.1136/bmjopen-2023-083414

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.

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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

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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

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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.

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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.

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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

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