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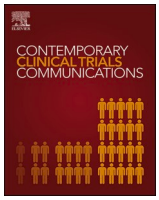

Effectiveness of nursing intervention to reduce delirium in adult critically ill - A protocol for a randomized trial

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ABSTRACT

The incidence of delirium in intensive care patients remains high, and its consequences have a high negative impact on patients, their families, health care teams, and society in general. Because delirium can lead to increased hospital stay, increased days on mechanical ventilation, increased risk of adverse events, increased memory loss and even increased mortality. However, some factors that precipitate delirium can be modified to reduce its presence and duration through non-pharmacological measures. Thus, the present protocol seeks to establish the theoretical and methodological background to develop and test nursing interventions to reduce delirium in adult patients hospitalized in the intensive care unit. For this reason, it is based on the theoretical elements of delirium and a nursing theory, called the Dynamic Symptoms Model (DSM), to understand the phenomenon and how nursing knowledge can be used to intervene. Thus, a nursing intervention proposal is proposed based on the DSM and scientific evidence, and a methodological design of a randomized controlled clinical trial type with parallel groups, which allows measuring the effectiveness of the designed interventions, following methodological and ethical rigor and with adequate control of biases.

1. Introduction

Delirium is a cognitive disorder with acute onset and fluctuating course, characterized by reduced ability to pay attention to the environment, impaired memory, disorientation, impaired language and perception, and impaired judgment [1]. Its onset varies between 20 and 90% in patients hospitalized in the Intensive Care Unit (ICU) with a duration between 1 and 5 days [2–4].

Several studies have found that the etiology of delirium is associated with predisposing and precipitating factors. Among the predisposing factors is age, mainly in people over 50 years old [5–7]. Also, antecedents of diabetes, atrial fibrillation [5], gastritis [5], chronic renal disease [8], postoperative states, arterial hypertension, inflammatory markers [7,8], elevated BUN, elevated creatinine [5], and sodium [5,9,10].

Among the precipitating factors have been found, such as mechanical ventilation, antipsychotic, benzodiazepines, and [3,11,12], antipsychotics, benzodiazepines, low scores in the Richmond Agitation-Sedation Scale (RASS) [3,6,12], pain, stress, disruption of the sleep-wake cycle, presence of physical immobilization [11,13–17], and medical devices [7,15]. These factors are specific to the ICU environment and treatment and increase the risk of developing delirium, regardless of the presence or absence of predisposing factors. However, precipitating factors are modifiable according to the diagnosis and evolution of the patient.

Heras La Calle [18] affirms that adequate management of pain, anxiety, and delirium improves the evolution of critically ill patients in the short and long term and reduces mortality. Thus, the high incidence and consequences of delirium continue to be of concern. For this reason, the American Guidelines of 2018 [19] and German 2015 [13] for the management of agitation, pain, and delirium, recommend monitoring and prevention of delirium, including non-pharmacological measures, which is part of the strategy of humanization of care in the ICU [18].

Thus, nursing has a predominant role in the approach to delirium. Moon et al. [20], Von Rueden et al. [12], and Donovan et al. [21] state that nurses' assessment and interventions are fundamental to prevent and treat delirium, as they are leaders in clinical decision making, communicate with patients, evaluate their conditions and their clinical outcomes consistently [21,22]. Therefore, nursing interventions can minimize the risk of delirium and reduce prolonged ICU stay, mortality, and long-term cognition impairment [12].

Therefore, it is important to develop strategies that reduce precipitating factors to create an environment that avoids delirium, provides

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more humanized care, focuses on the personal needs of patients and their families. On the other hand, the predisposing factors of delirium suggest a baseline or possible confounding variables to detect and control.

For this reason, we analyze the characteristics of delirium from a nursing theory to find theoretical support that addresses its intervention. Thus, we use the Dynamic Symptoms Model (DSM), developed by Brant et al. [23]. DSM has four fundamental and structural elements (antecedents, experience and trajectory, interventions, and consequences) [24], which allow understanding and approaching delirium from a complete and unpartitioned perspective. A systematic review of the literature was done to contrast this theory and delirium (Fig. 1), finding convergence in their elements [25].

This research aims to determine the effectiveness of nursing interventions based on the DSM and scientific evidence, compared to daily care, for reducing the incidence and duration of delirium in people hospitalized in the adult ICU. Therefore, the study hypothesis is: Nursing intervention based on the DSM and scientific evidence effectively reduces the incidence and duration of delirium in patients hospitalized in the ICU.

2. Materials and methods

2.1. Type of study

The methodology to achieve the goal of this study is a double-blinded randomized control trial of parallel groups, phase III [26]. This trial evaluates the effectiveness and safety of the intervention designed in a special population, such as the ICU population, who are at higher risk of developing delirium. Fig. 2 represents the overall study design.

2.1.1. Population

The target population is the patients admitted to the adult ICU of a health institution in Colombia during the time of execution of the study.

2.1.2. Eligibility criteria

The inclusion criteria are: being admitted to the ICU, being over 18 years of age, accepting to participate in the study by signing an informed consent form, not having delirium at the time of recruitment, and having a family member or caregiver who visits them regularly. In addition, who have cognitive or neurological disorders, and who have RASS -5 o +4 were excluded.

2.1.3. Sample size and type of sampling

The type of sampling is probabilistic and random through permuted blocks of six blocks by three permutations, randomly assigned in the Excel program.

The formula the asymptotic normal method for two comparison groups, developed by Hahai H. and Khurshid A. [27], is used to calculate the sample size. One group receives the new treatment, and the other is the control group, who receives daily therapy in the ICU. We established a 1:2 ratio between the intervention and the control groups to reduce the measuring bias in front of the transferring information possibility when participants, family, or members of the health team, can apply some care or activities given to the participants of the intervention group.

According to a previous study at the same institution, the expected proportion of delirium in the group treated with the new intervention is 6%, while the daily treatment is 21.8% [15]. Therefore, it is considered that the new treatment is better than the daily treatment, so the one-tailed hypothesis is followed.

$$n = n_1(k+1)$$

where

$$n_1 = \frac{\left(Z_{1-\frac{\alpha}{2}}\sqrt{\underline{P}(1-\underline{P})(1+1/k)} + Z_{1-\beta}\sqrt{P_c(1-P_c)+P_n(1-P_n)/k}\right)^2}{(P_c-P_n)^2}$$

$$\underline{P} = (P_c + kP_n) \;/\; (k+1)$$

The following formula was used to calculate the power according to

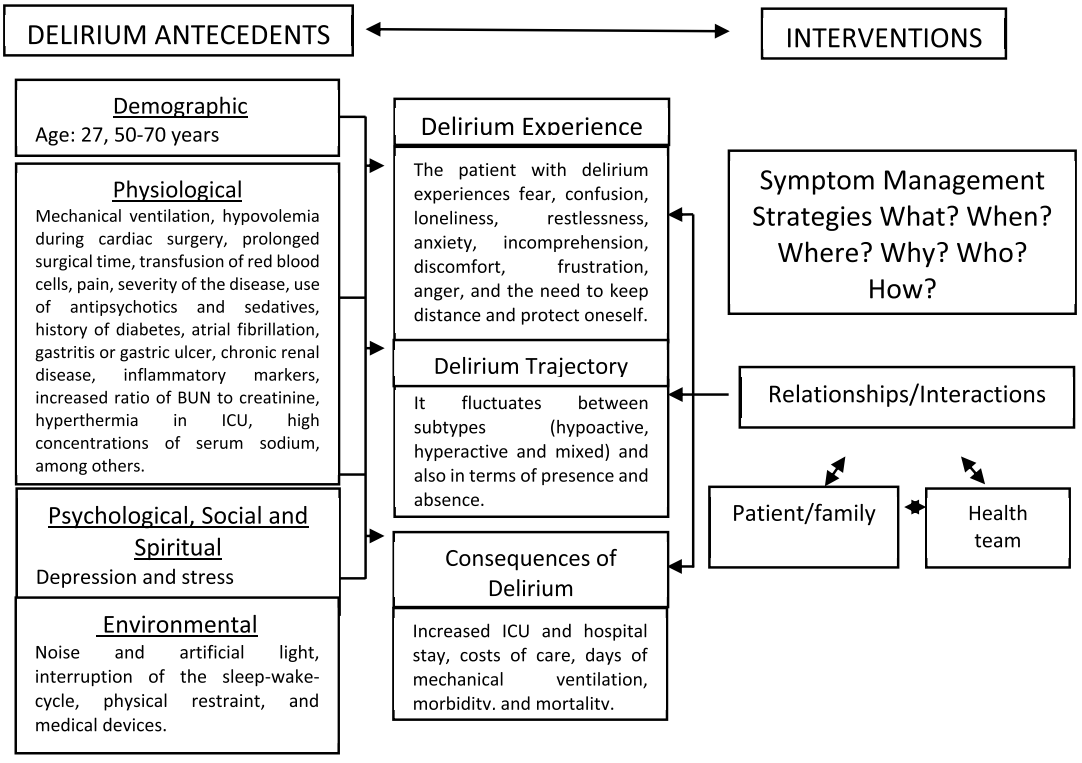

Fig. 1. Analysis of delirium from the DSM.
Source: Taken from Analysis of Delirium from Dynamic Symptoms Model [34].

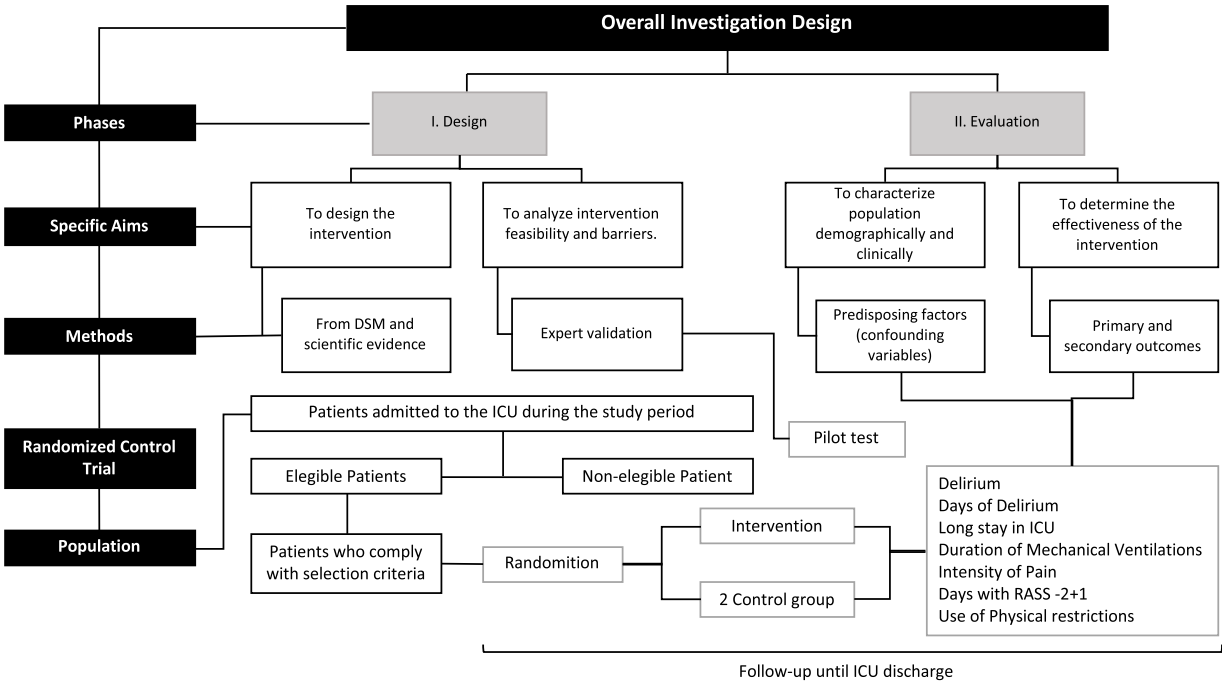

Fig. 2. The general design of the study.

the sample size:

1-β = Φ ($Z_{1-\beta}$) where

$$Z_{1-\beta} = \frac{\sqrt{\frac{n(P_c-P_n)^2}{k+1}} - Z_{1-\frac{\alpha}{2}}\sqrt{\underline{P}(1-\underline{P})\left(1+\frac{1}{k}\right)}}{\sqrt{P_c(1-P_c)+\frac{P_n(1-P_n)}{k}}}$$

The parameters for the formula are:

α 0.05; β = 0.20; k = 1 to one tail.
Pn = 0.06 (Expected proportion in the intervention group)
Pc = 0.21 (expected proportion in the control group)

The ratio of 2 controls for each intervention, with 95% reliability and 90% power. Replacing the values, we have 71 patients for the intervention group and 142 for the non-intervention or control group, to 213 participants. We considered the possible losses by dead or early discharge before 48 h in ICU, increasing the sample size by 10%, resulting in 234 patients.

2.1.4. Masking

The study is double-blind since the participants and their relatives, the research assistant who measures the study and outcome variables, will be unaware of the assignment of the control and intervention groups. Thus, research assistant 1 is the one who performs the randomization, assigning the participants to one of the three groups, A, B, and C (two control groups and one intervention group), according to the sequence of permuted blocks.

2.1.5. Study phases

The establishment of the phases of the study is carried out following the main criteria proposed by Sidani and Braden [28], which are:

2.1.6. Phase I. Design

•Intervention Design. This phase includes analysis of the problem to be intervened (reduction of the incidence and duration of delirium) and the design of nursing interventions based on scientific evidence and DSM. The level of evidence is classified according to The Grading of Recommendations Assessment, Development and Evaluation (GRADE), adopted by the World Health Organization (WHO) and Cochrane Library [29].

•Analysis of the feasibility, viability, and barriers of the intervention designed through validation by experts in the field working in the institution.

Phase II. Evaluation of the Intervention.

•Pilot test to 10% of the sample.

- Assessment of the ideal conditions for the application of the intervention. Assessment of mechanisms to control confounding biases, which in this case corresponds to the predisposing factors of delirium (age, comorbidities, diagnosis, sepsis, sodium levels, BUN, creatinine, body temperature, glycemia).
- Identification of unanticipated findings. Search for conceptual and methodological factors that could explain the results.
- Assessment of the risks derived from the intervention.

•Effectiveness evaluation. The extent to which the intervention produces the intended beneficial results.

These phases agree with the elements of complex intervention research presented by the Medical Research Council [30]. They suggest implementing four phases: development or identification of the intervention, feasibility, evaluation, and implementation. The first is concordant with our design phase. The second (feasibility) is developed in this study with the pilot test. The third (evaluation) corresponds with our phase of effectiveness evaluation with the clinical trial. And fourth phase implementation will be recommended for future study because our scope and funding close-out with effectiveness test.

2.2. Intervention

We followed the recommendations of Sidani and Braden to develop the nursing intervention. For this reason, "Dynamic Delirium" (DyDel) was constructed based on the DSM and scientific evidence. The DSM and the theoretical aspects of delirium allowed us to find the domains, components, and elements to intervene. DSM gives structure and support to take and provide intervention covering the patient in his totality,

physical, psychologic, spiritual, social, and environmental antecedents, with an experience of symptoms and trajectory (see Table 1).

The scientific evidence provided the care to be applied. To select the care of scientific evidence, we carried out a systematic review that reflected the main interventions and their effectiveness [31]. Table 1 summarizes the DyDel components.

Intervention group: the participants of this group receive Dynamic Delirium. We follow TIDieR (Template for Intervention Description and Replication) recommendations [32] to describe DyDel intervention. TIDieR has 12 items, 1. name, 2. why, 3. materials, 4. procedures, 5. who provided, 6. how, 7. where, 8. when and how much, 9. tailoring, 10. modifications, 11. how well planned, and 12. how well actual. In this study, the last two items were not applied. Table 2 specify each item.

Control group: The control groups will receive the nursing interventions that are performed daily in the adult ICU of the institution, orientation in time, space, and place, accompaniment of the family for 2 h in the morning and 2 h in the afternoon, physical therapy once a day according to the patient's condition, medication with conscious sedation, and the progressive reduction of opioid analgesics and benzodiazepines.

Every care and activity of DyDel will be given inside the individual ICU cubicle of intervention group patients to avoid the control group receiving part of the intervention. Further, the nurse and the family who will apply the intervention will sign a confidentiality agreement to reduce the possibility of transferring information about the intervention to other patients and families of the control group.

2.3. Outcomes

The primary outcome variables are:

- Percentage Incidence of delirium.
- The number of days of delirium.

The secondary outcome variables are:

- The number of days of stay in ICU.
- The number of days on mechanical ventilation.
- Pain intensity (according to VAS and Campbell scale).
- RASS scale between −2+1.
- The number of days with the use of physical restraints.

Participant timeline

The schedule for recruiting and conducting interventions and evaluations is shown in Fig. 3.

2.3.1. Instruments

- Format for recording the sociodemographic and clinical variables, predisposing factors of delirium, and primary and secondary outcome variables used to measure the effectiveness of the intervention. It contains three chapters: 1. Sociodemographic characteristics with three items, 2. Clinical features - predisposing factors with 25 items, and 3. Effectiveness of the intervention with eight items; for a total of 36 items.
- RASS: Richmond Agitation Sedation Scale designed and validated in 2002 [33]. It is validated in Colombia [34] and has nine options: −5 Profound sedation, −4 Deep sedation, −3 Moderate sedation, −2 Light sedation, −1 Drowsy, 0 Alert calm, +1 Anxious restless, +2 Agitated, +3 Very agitated, and +4 Combative or violent.
- CAM-ICU: Confusion Assessment Method for Intensive Care Unit. Adapted and validated for ICU patients by Wesley et al., in 2001 [35]. Validated in Colombia by Toro et al. [36]. It has two result options: positive or negative for delirium.
- VAS: Visual Analog Scale. The unidimensional method that assesses the intensity of pain numerically, starting from 0, which represents

Table 1
Summarize of domains, components, care and activities of intervention "Dynamic Delirium" (DyDel).

DSM Domain	DSM Components	Delirium aspect to intervene (care)	Activities
Physiologic antecedents	Medical condition	1. Pain reduction	4 Measuring pain with VAS or Campbell scales, each/2 h (By nurse). 4 Assess signs of pain, each/2 h (By nurse). 4 Verify analgesia and last dose if pain (By nurse). 4 Verify and eliminate possible sources of pain each shift (By nurse). ϑ Music and relaxation therapy on-demand (By nurse or family).
		2. Awakening and spontaneous breathing	4 Allowing family companionship during awakening (By nurse). 4 Educate on spontaneous breathing (By nurse). 4 Mobilize the patient each shift (massage, bed exercises, chair sitting, standing, small steps) (By nurse and family).
	Treatment	3. Level and goal of sedation	4 To ask daily sedation goal, each shift (By nurse). 4 RASS valuation each 2 h (By nurse).
Psychological, spiritual and social antecedents	Psychologic (knowledge and personality)	4. Cognitive estimulation	4 Orientation on the date, time, and place (each shift) (By nurse and family). 4 Prolong family company at least 5 h/day (By nurse). 4 Facilitating assertive communication with the family (By nurse and family). 4 Allow use of glasses and hearing aids if required (By nurse and family). ϑ Develop occupational activities with family (reading the newspaper, books, solving crossword puzzles, listening to music or radio, drawing or coloring) (By nurse or family).
		5. Preferences – stressors	ϑ Identify and allow for preferred routines and activities (By nurse and family). ϑ Allow objects of preference to provide comfort (By nurse and family).
	Spirituality	6. Spirituals necessities	ϑ Identify and resolve spiritual needs, to keep spiritual objects like rosary, books, bible, calling or visit of priest

(continued on next page)

Table 1 (*continued*)

DSM Domain	DSM Components	Delirium aspect to intervene (care)	Activities
			or pastor (By nurse and family).
	Social	7. Social support	ϑ Identify and solve social needs, like calling or visits of friends, colleagues, extent family, letters of friends (By nurse and family).
Environmental antecedent	Physical	8. Physical environment in the ICU	ϑ Identification of environmental stressors (By nurse and family). ϑ Noise reduction at night (By nurse). ϑ Provide earplugs for sleeping (By nurse or family). ϑ Keep light on during the day to promote alertness (By nurse) ϑ Reduce artificial light at night (By nurse). ϑ Provide eye band for sleeping (By nurse or family).
Experience	Symtomps	9. Identification of other symptoms	4 Identify and resolve fear, confusion, restlessness, loneliness, moodiness, and discomfort related to care and environment (By nurse).
Trajectory	Delirium assessment	10. Timely identification of delirium.	4 Apply CAM-ICU scale each shift (By nurse).

Abbreviations: DSM, dynamic symptoms model; VAS, visual analogue scale; RASS, Richmond agitation sedation scale; ICU, intensive care unit; CAM-ICU, confusion assessment method for the intensive care unit.
4 Mandatory activities J Optional activities according to the patient's preferences.

no pain, and up to 10, which corresponds to the worst pain imaginable. Values lower than 4 mean mild or moderate pain, between 4 and 6 mean moderate, severe pain, and higher than 6 means very severe pain [37]. It is a widely used scale, even in patients hospitalized in the ICU [38–40].

- CAMPBELL SCALE: measures pain and its intensity, is recommended for non-communicative critical patients [38,41]. This scale evaluates five behavioral items: facial musculature, calmness, muscle tone, verbal response, and comfort. Its cut-off points allow a numerical classification of pain from 0 to 10, where 0 is no pain, 1 to 3 is moderate pain, 4 to 6 is severe pain, and more than 6 is maximum pain [37]. This scale has cross-cultural adaptation and adequate validation and reliability in Colombia [42].

The description of all study variables and outcomes measures is presented in Table 3.

2.3.2. Data collection procedure

Method: The unit of analysis and information is the patients and their clinical histories. A data collection format will be applied where the study variables are specified.

Technique: The technique to be applied to measure the effectiveness of the interventions corresponds to the review of clinical histories and observation. Research assistant 1, Registered Nurse (RN), recruits the participants on the day of admission to the ICU and verifies whether they meet the selection criteria. Then, she randomly assigns them to one of the intervention or control groups according to a permuted block distribution (six blocks of three, with groups A, B, and C: two control and one intervention). Subsequently, she informs research assistant 2 (RN specialist in critical care) which patients the intervention should be performed.

Research assistant 1 also informs research assistant 3 (RN specialist in critical care) which patients are part of the study, without informing them of the assigned group, only its nomenclature (A, B, or C). Research assistant 3 follows up on each shift and assesses the confounding and outcome variables. Research assistant 3 performs the follow-up at a different time than research assistant 2 in order to maintain masking and prevent measurement bias. The follow-up and interventions will be performed until the patient is discharged from the ICU.

2.3.3. Tabulation and analysis plan

Tabulation: the information will be recorded manually in printed formats and then entered into a Microsoft Excel database for export to the data processing software. The information will be entered twice to minimize measurement bias.

Analysis: not all participants of the intervention group will receive the complete intervention because five care are optional according to patient preference. For this reason, we will follow a sensitivity analysis to assess the strength of the results to protocol divergence [43]:

- Sensitivity analysis 1. It will be based on an intention-to-treat analysis, from which the analysis process keeps the original group assignment to preserve the balance of randomization [44].
- Sensitivity analysis 2. Analysis with and without adjustment for baseline characteristics. If we find significative differences in baseline characteristics between study groups, we will conduct a multivariable regression vs. propensity score method distributional.
- Sensitivity analysis 3. We will use a hazard model to reduce competing risk.
- Sensitivity analysis 4. We will apply a comparative analysis of distributional assumptions, with distribution Poisson vs. negative binomial.
- Sensitivity analysis 5. Parametric vs. non-parametric methods will be used to analyze outcomes variables between groups.
- Sensitivity analysis 6. A distribution analysis over time to develop delirium will be done with an accumulative risk, considering proportional risk assumptions.

Further, the patients who will die and who will discharge from the ICU 48 h after recruitment will be excluded.

Statistical analysis: the demographic and clinical characteristics of each of the participants in the groups will be described using frequencies and proportions for qualitative variables, central tendency, and dispersion for quantitative variables after normality test with Shapiro-Wilk and Kolmogorov Smirnov tests. If the data do not have a normal distribution, it will be described by median and interquartile ranges.

A one-way ANOVA test will compare the results between the two groups for the mean difference when the data are normally distributed. Still, if the data are not normally distributed, we will use non-parametric statistics (Kruskal-Wallis test). We will calculate the Z test to find the difference of proportions for qualitative variables. Pearson's chi-square will be calculated when the criteria are met (expected values > 5 in each cell); otherwise, Fisher's chi-square test will be applied.

Relative risk (RR) will be calculated to establish the decrease in the risk of delirium and Kaplan Meier curve for the analysis of survival to delirium in both groups. We will use the stepwise technique to choose the covariables in the regression model, with an input probability of 0.3 and an output probability of 0.1, starting from the variables described in the literature as predisposing to delirium and those that showed statistically significant differences. The models constructed will be evaluated

Table 2
Description of TIDieR guideline recommendations of DyDel intervention.

Items of TIDieR		DyDel intervention
1. Name	Name or a phrase that describes the intervention.	Dynamic Delirium
2. Why	Describe theory or goal of the intervention.	focused in non-pharmacological interventions to prevent and treat delirium, because these are recommended by different guidelines [13,19] bundle ABCDEF [31] and in the HU-CI project (Humanization of ICU by its acronym in Spanish) [18].
3. Materials	Materials used in the intervention delivery.	We used books, magazines, radios, board games, tablets to see movies, eye bands, ear plugs, and others patient preference. Also, we can identify in due time pain and delirium, we can use validate scales VAS or Campbell, RASS, and CAM-ICU.
4. Procedures	Procedures, activities, and/or processes used in the intervention.	If the patient is in RASS between −1 and 2: The nurse starts measuring and reducing pain (care 1), delirium (care 10), and related symptoms (care 9). Then, the nurse and the family member give the patient cognitive stimulation (care 4), reduce stress by providing comfort (care 5), and identify and resolve spiritual (care 6), social (care 7) and environmental necessities (care 8). If the patient is in RASS between −2 and 4: The nurse starts measuring and reducing pain (care 1) and delirium (care 10) and talks with the health team about the daily sedation goal of the patient (care 3). Then, the nurse and the family member promote the patient awakening and spontaneous breathing (care 2). And they give the patient cognitive stimulation (care 4), reduce stress by providing comfort (care 5), and identify and resolve spiritual (care 6), social (care 7) and environmental necessities (care 8).
5. Who provide	Describe their expertise, and specific training given.	Nurse specialist in intensive care
6. How	Modes of delivery	Face-to-face
7. Where	Describe the type(s) of location(s) where the intervention occurred.	Intensive care units.
8. How much	Number of times the intervention was delivered.	DyDel intervention was delivered diary, considering the kind of activities (See Table 1). Nurse and family member planned the activities for each shift. The duration of occupational activities changed according to the patient's preferences.
9. Tailoring	If the intervention was personalised, titrated or adapted.	DyDel intervention was personalised according to the patient's preferences and health condition.
10. Modifications	If the intervention was modified during the course of the study.	The intervention does not suffer modifications during the study.

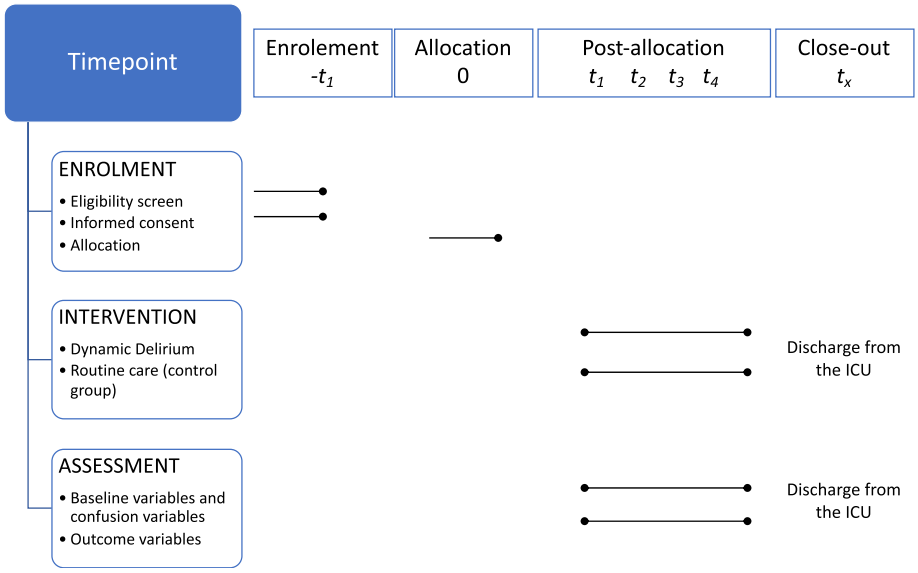

Fig. 3. Description of time schedule of clinical trial process according to SPIRIT guidance.

by re-estimation and Hosmer and Lemeshow tests. All tests will be significant at a $p \leq 0.05$, and analyses will be performed using STATA® 16.1 and SPSS version 28 software.

2.3.4. Bias control

Bias control for the present study will be carried out taking into account the approaches of Manterola et al. [45] and Hernández et al. [46] as follows:

•Selection bias. It is controlled by:
- Population: all participants were selected from the same population, the adult ICU of a hospital in Colombia. Participation is voluntary and according to selection criteria.
- Sample: its calculation has a reliability of 95% and a power of 80%, figures recommended to achieve representativeness.
- Probabilistic and random sampling type.
- Masking: patients, their families, and the research assistant nurse 3, who measures the outcome variables, will be unaware of the group assignment.
- Losses are tolerated at a maximum of 20% and correspond to those who request and sign the waiver form.

•Information or measurement bias. It is controlled by:
- Masking
- Double entry of the information and review of their differences, guaranteeing its analysis and correction.

Table 3
Variable description and outcomes measures.

TYPE OF VARIABLES	FACTORS	VARIABLES	OPERATIONAL DEFINITION	SCALE OR CATEGORY	
Confuser	Demographic characteristics	Age	Patient's age at the time of application of the questionnaire.	Years	
		Sex	Classification according to the sex of the participant.	- Man - Woman	
Confuser	Pathological aspects	Pathology	The medical diagnosis for which the patient was admitted to the ICU.	Description of ICU admission diagnosis.	
		Comorbidities	Pathological history of the patient at the time of admission to the ICU.	- Arterial hypertension - Diabetes Mellitus - ERC - Cancer - Delirium - F.A - Gastritis - ACV - Sepsis or any infectious condition - Other.	
		Psychoactive history	History of consumption of legal and illegal psychoactive substances	- Smoking - Alcoholism - Illicit drug use (marijuana, cocaine, or other)	
		Cardiothoracic surgery	Cardiothoracic surgery requirement immediately before ICU admission and the study.	YES NO	
		Orthopedic surgery	Requirement for orthopedic surgery immediately before ICU admission and the study	YES NO	
		Blood transfusion	Performance of ERG transfusion in recent hospital stay, before or during ICU stay.	YES NO	
Confuser	Aspects of hospital stay	Place of hospitalization	Service in which the patient was hospitalized before admission to the ICU.	- Hospitalization surgery - Internal medicine hospitalization - Neurosurgical hospitalization - Obstetrics and gynecology hospitalization - Transplant hospitalization - Psychiatric hospitalization - Infectious disease hospitalization - Emergencies - Observation - Surgical Rooms	
		Delirium in current hospital stay	Presence of delirium in current hospital stay before ICU admission	YES NO	
Confuser	Biomarkers	Serum sodium	Serum sodium level at study entry and daily measurement	mEq/L	
		Glycemia	Glycemia level at study entry and daily measurement	mg/dL	
		Temperature	Body temperature level at study entry and daily measurements	°C	
		BUN	Blood urea nitrogen level at study entry and controls as required.	mg/dL	
		Creatinine	Creatinine level at study entry and controls according to requirements	mg/dL	
		Leukocytes	Number of leukocytes at study entry and controls as required.	mm^3	
Confuser	Pharmacological aspects	Sedatives	Type of sedative medication administered during ICU stay.	- Midazolam - Propofol - Dexmedetomidine - Ketiapine	YES/ NO
		Analgesics	Type of analgesic medication administered during ICU stay.	- Morphine - Fentanyl	YES/ NO
		Antipsychotics	Type of antipsychotic medication administered during ICU stay.	- Haloperidol - Risperidone - Quetiapine - Olanzapine	YES/ NO
Confuser	Aspects of ICU care	Physical restrictions	Use of physical restraints or immobilizations at study entry and daily measurement	YES NO	
		Medical devices	Presence of medical devices at admission and daily measurement	- Central venous catheter - Bladder catheter - Nasogastric tube - Arterial line - Mahurca catheter - Intra-aortic balloon	YES/ NO
Primary Outcome	Presence of delirium	CAM-ICU	The CAM-ICU scale assessment results upon admission to the ICU and measurement every shift during the study period.	Positive for delirium Negative for delirium	
		Duration of delirium	The number of delirium days from diagnosis (CAM-ICU or Nursing Delirium tests positive).	Hours Days	
	Level of sedation	RASS		−5 Unarousable	

(*continued on next page*)

Table 3 (*continued*)

TYPE OF VARIABLES	FACTORS	VARIABLES	OPERATIONAL DEFINITION	SCALE OR CATEGORY
Secondary Outcome			The RASS scale assessment results upon admission to the ICU and measurement every shift during the study period.	−4 Deep sedation −3 Moderate sedation −2 Light sedation −1 Awakens to voice 0 Alert and calm +1 Anxious, apprehensive +2 Frequent nonpurposeful movement +3 Aggressive +4 Combative, violent
Secondary Outcome	Assessment of presence and intensity of pain	VAS: Visual Analog Pain Scale.	According to numerical distribution, pain intensity rating is used for conscious patients who can respond (0–10).	0 absence of pain <3 mild pain (2 little pain) 3-7 moderate pain (4 moderate pain, 6 severe pain) 7-10 severe pain (8 very severe pain, 10 the worst imaginable or unbearable pain)
		Campbell Scale	According to numerical distribution, pain intensity classification is used in non-communicative critical patients (0–10).	0 absence of pain 1-3 mild to moderate pain 4-6 moderate to severe pain >6 very severe pain
Secondary Outcome	Mechanical ventilation	Days on mechanical ventilation	The number of mechanical ventilation days from the date of admission to the ICU and the study.	Hours Days
Secondary Outcome	ICU stay	Length of stay in ICU	The number of days in the ICU from ICU admission until patient's discharge of ICU.	Hours Days

- Confidentiality agreement: family members of participants will be asked to sign a confidentiality agreement.

•Confounding bias: Controlled by:

- Measurement of confounding variables: corresponding to the predisposing factors of delirium.
- Exclusion criteria: this allows for a population without psychiatric and cognitive pathologies that could confound the diagnosis of delirium.
- Randomization: avoids problems of comparability between groups.
- Multivariate analysis: controlling for confounding variables to estimate the effect of exposure.

3. Ethical issues

The present research has the endorsement of the ethics committee of the Faculty of Nursing of the National University of Colombia (AVAL 002–21, February 16, 2021) and of the ethics committee of the hospital where the study is carried out (Endorsement No. 001–005 of January 26, 2021). The ethical guidelines set forth in the international regulations are followed:

- Declaration of Helsinki [47] The integrity of the participants and their families are respected, as they are informed about the study's objectives and the freedom to participate and sign a consent form.
- Belmont Report [48] Autonomy is guaranteed because each participant can leave the study whenever they wish. Beneficence because the participants in the control group receive the designed intervention once they leave the research and in the long term with the social value generated by the study.
- International Ethical Guidelines for Health-Related Research Involving Human Subjects [49] are defined by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO). Relevant and plain language information about the study is provided to patients and their families. In addition, how patients under sedation are considered vulnerables, their family members will sign the consent form. When the patient regains their capacity, they are asked to sign the consent to continue their participation if they wish to do so.

About Colombian regulations for the execution of investigations, the requirements are complied with as follows.

- Resolution N° 8430 of 1993 [50]. According to article 11, this research is classified with a risk higher than the minimum. The possible risks represented by the intervention were analyzed, which are minimal, do not threaten the patient's safety and stability, and can be immediately mitigated.
- Law 911 of 2004 [51]. This study complies with the requirements of informed consent, and the dignity, integrity, and rights of the participants are safeguarded.
- Law 1581 of 2012 [52] and Decree 1377 of 2013 [53] on data protection. Only researchers will review the data, they will be disclosed only in a scientific manner without including the identity of the participants and the Institution. The database is not published on the Internet or used for other studies.

Author contributions

The present clinical trial protocol has been developed in its entirety by the authors who contributed to the study design and commented on the manuscript. GT wrote the manuscript, conceptualized the study, obtained the funding, developed the theoretical framework, and developed the analysis plan. HC reviewed and adjusted study design, theoretical conceptualization, analysis plan, and supervise the entire research process.

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Trial registration

Clinicaltrial.gov code: NCT05172583.

Protocol version

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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