Supplementary Table S1: SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	page/line numbers
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/Line1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3/Line43-44
	2b	All items from the World Health Organization Trial Registration Data Set	Not applicable
Protocol version	3	Date and version identifier	P6/Line 95-96
Funding	4	Sources and types of financial, material, and other support	P22/Line394-398
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/Line5-17 and P21/Line378-383
	5b	Name and contact information for the trial sponsor	P1/Line5-8 and the registration information.
	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	P22/Line395-399
	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)	Detail in aggrement
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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P5/Line60-P6/Lline90
	6b	Explanation for choice of comparators	P5/Line68-76 And P18 Line319-321
Objectives	7	Specific objectives or hypotheses	P6/Line87-90

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)	P6/Line93-96
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	P6/Line98-P7/Line101
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)	P7/Line104-P8/Line131
Interventions	11a	Interventions for each group with and sufficient detail to allow replication, including how when they will be administered	P10/L158-P11/Line193
	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)	P11/Line185-194
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P12/Line194-P13/Line218
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/L233-P15/L258
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)	Supplementary Table S3
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	P15/Line271-P16/Line284
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P9/Line133-138
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	P9/Line142-144
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	P9/Line143-149
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P9/Line144-149
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P9/Line151-P10/156
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
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	P13/Line 224-231 And The handbook for researchers
	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	P13/Line 220-222
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	P13/Line225-231 And The handbook for researchers
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	P16/Line286-P17/Line312
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P17/Line296-310
	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)	P16/Line286-288

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	P15/Line267-269
	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	P17/Line310-312
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	From P15/Line260-269
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	P21/Line390-393
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)	Not applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P9/Line133-139
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in the ICF
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	Detail in the ICF
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P21/Line385-388
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	Detail in aggrement
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	Detail in the ICF

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	P21/L392-393
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary document-ICF
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

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Supplementary Table S2: Criteria for discontinuation of esketamine hydrochloride

Event	Discontinuation criteria and management (esketamine hydrochloride)	Data processing
72 hours after randomization	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Patient or family member withdraw the informed consent	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Patient died	Stop esketamine hydrochloride infusion	Data will be included in the analysis
Analgesics are not required due to extubation or other medical reasons	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Require deep sedation or neuromuscular blockers	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Severe heart failure (EF<30%), cardiogenic shock or acute myocardial infarction	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the Electronic Data Collection System（EDC）	Follow up, data will be included in the analysis
Acute liver failure	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Renal dysfunction that probably caused by esketamine	Stop esketamine hydrochloride infusion, adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Require Surgery or tracheotomy	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Unable to accurately assess CPOT and RASS score	Stop esketamine hydrochloride infusion	Follow up, data will be included in the analysis
Uncontrolled agitation (pulling off artificial airway, tubes or lines and combative behavior)	If it is related to esketamine hydrochloride, the infusion stops; if not, the infusion continues. Adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis
Uncontrollable hypertension (SBP≥180mmHg, DBP ≥100mmHg) lasting more than 3 hours		
Other sever adverse events that the treating team believes may be related to esketamine hydrochloride	Stop esketamine hydrochloride infusion, the adverse event needs to be reported in detail and recorded in the EDC	Follow up, data will be included in the analysis

Esketamine hydrochloride infusion should be discontinued when any of the events listed in the table occur, whichever occurs first, but patient follow-up should continue.

Supplementary Table S3 : Study schedule

Time point	-D1	D0	D1	D2	D3	D4	D5	D6	D7	D...	D28
Enrolment											
Eligibility screen	×										
Informed consent	×										
Allocation		×									
Intervention											
Intervention of the standard care group		×	×	×	×						
Intervention of S-ketamine group		×	×	×	×						
Assessment											
Baseline demographics	×										
Diagnosis	×										
Comorbidity	×										
Mechanically ventilation duration before randomization		×									
Cumulative dose of sufentanil before randomization		×									
SOFA score		×	×	×	×	×	×	×	×		
APACHE-Ⅱ score		×							×		
AGI and enteral nutritional tolerance score（daily）		×	×	×	×	×	×	×	×		
Gastric residual volume and intra-abdominal pressure （every 12 hours）		×	×	×	×	×	×	×	×		
Liver function, renal function, and myocardial enzymes		×	×	×	×				×		
RASS and CPOT（every 4 h）		×	×	×	×						
Cumulative dose of sufentanil		×	×	×	×		×				
Cumulative duration of sufentanil		×	×	×	×		×				
Cumulative dose of esketamine hydrochloride		×	×	×	×						
Cumulative duration of esketamine hydrochloride		×	×	×	×						
Cumulative dose of propofol, midazolam and dexmedetomidine		×	×	×	×						

Cumulative duration of propofol, midazolam and dexmedetomidine		×	×	×	×						
Require for frequent suctioning			×	×	×						
Uncontrolled agitation			×	×	×						
Nutrition implementation						×			×		
CAM-ICU and psychotropic drugs used for delirium			×	×	×	×	×	×	×	×	×
Adverse events, severe adverse events and adverse events that may related to study drug			×	×	×	×	×	×	×	×	×
Ventilation free day			×	×	×	×	×	×	×	×	×
Vasopressor free days			×	×	×	×	×	×	×	×	×
Length of ICU stay			×	×	×	×	×	×	×	×	×
Length of hospital stay			×	×	×	×	×	×	×	×	×
28-day mortality rate after randomization			×	×	×	×	×	×	×	×	×