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A COMPARISON OF DEXMEDETOMIDINE vs. PLACEBO EFFECT ON SLEEP-QUALLITY IN MECHANICALLY VENTILATED CRITICAL ILL PATIENTS: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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Abstract:

Introduction: Sleep deprivation, which is a common complication in the ICU, is associated with delirium and increased mortality. Sedation with GABA agonists (Propofol, Benzodiazepam) results in significant disturbance of the sleep architecture, including suppression of SWS (Slow Wave Sleep) and REM (Rapid Eye Movement) sleep. Dexmedetomidine is a lipophilic imidazole with an affinity for α_2-adrenoceptors and it has sedative and analgesic properties. It has been reported to enhance SWS, thus sedate while preserving sleep architecture.

Methods and analysis: Thirty consecutive patients are planned to be included, at the department of Anesthesia and Intensive care at the Hospital of Southwest Jutland, Denmark. The study is a double blinded, randomized, controlled trial with two parallel groups (2:1 allocation ratio).
Screening and inclusion are done on day one from 8.00 to 16.00. Two 16 hours PSG (polysomnography) recording are done starting at 16.00 on day one and day two. Randomization is performed after if the first recording is of acceptable quality, otherwise the patient is excluded. Dexmedetomidine/placebo is given during the second recording from 18.00 day two to 6.00 day three. **Primary endpoint:** Improvement of SWS /sleep quality of clinical significance determined SWS activities. **Secondary endpoints:** Sleep phases determined by PSG and daytime function including anxiety and delirium determined by Cam ICU. Alertness and wakefulness determined by RASS. The objective is to compare the effect of dexmedetomidine vs. placebo on sleep-quality in critical ill mechanically ventilated patients.

Ethics and dissemination: The trial investigate the potential benefit of Dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients and publication in peer reviewed journal are planned. The study has been approved by the local ethical committee.

Strength and limitation

The study is an investigator-initiated randomized placebo controlled double blinded trial, but due to the nature of the study drug, we expect in some cases that the patient's sedations level drops radically, after administration of the study drug/placebo, hence a risk of unblinding the trial.

Introduction:

Sleep disturbance in mechanically ventilated critically ill patients is a common complication [1-4]. About 50 percent of ICU patients report disturbed sleep and one-third continues to suffer from poor sleep quality 6-12 months after discharge [5]. Patients reports sleep-wake disorganization, sleep fragmentation and abnormal sleep architecture with increased stage 1 and stage 2 non-rapid eye movement (NREM) sleep, decreased stage 3 (slow wave sleep (SWS)) and rapid eye movement (REM) sleep [1-4]. Sleep deprivation is associated with dysfunction of the immune and cardiovascular systems, disturbed metabolism, impaired memory, delirium, and in turn increased mortality [6-8]. Sedatives and analgesics are often administered to the critically ill patient to increase comfort, decrease anxiety and promote sleep. There are two commonly used classes of sedatives: benzodiazepine and propofol interacting with the gamma-aminobutyric acid (GABA) receptor and those with an affinity for alpha-2 receptors in the locus coeruleus, such as dexmedetomidine [2]. Infusing propofol and midazolam induce sleep and the perception of sleeping [4 9], however sedation with GABA agonists results in significant disturbance of sleep architecture, including suppression of SWS and REM sleep [1-4]. Administration of GABA agonists, especially benzodiazepine, has been reported to cause delirium, prolong mechanical ventilation and ICU stay [7 10]. For several years the standard practice for sedation of patients in need of mechanical ventilation has been a combination of opioids and intravenous infusion of benzodiazepines and/or propofol. This strategy is known to prolong MV, weaning from the ventilator and LOS in ICU and hospital [11 12]. Recent guidelines [13 14] have advocated a revision of ICU sedation practices towards optimal patient comfort with minimal sedation [14] to improve clinical outcomes in mechanically ventilated adult ICU patients. As a result light or non-sedation has been applied to avoid affecting sleep architecture and delirium and previous data demonstrate that comfort during mecanical ventilation (MV) can be achieved with no or very light sedation, which is associated with lower incidences of delirium and shorter Lengh of Stay (LOS) in ICU [15-18].

Dexmedetomidine is a lipophilic imidazole derivative with an affinity for α_2-adrenoceptors 1600 times higher than for α_1-adrenoceptors and 8 times higher than the prototype α_2 agonist drug, clonidine [19]. It has sedative and analgesic properties and can be used as an alternative in cases where non-sedation is not applicable. It has been reported to inhibit the release of norepinephrine in the locus coeruleus as well as enhancement of SWS by mimicking the endogenous NREM sleep pathway [20]. Dexmedetomidine activates central pre- and postsynaptic α_2-receptors in the locus coeruleus, thereby inducing a state of unconsciousness similar to natural sleep – resemplilng NREM

sleep [21]. The action involves an inhibition of the reticular activation system primarily involving cortex but to lesser degree cardio-pulmonary function. This unique site of action lends Dexmedetomidine an equally unique sedative profile, conferring ability to sedate while at the same time allowing for patient arousability and interaction with relatives and staff. As a sedative, Dexmedetomidine is notable for its lack of respiratory drive suppression [22].

The minimal sedation strategy has among other conditions revealed sleep disturbances especially during night time. Dexmedetomidine, has been shown to provide good comfort during MV with a good safety profile [23-25] and reduced time to extubation [12]. In addition previous studies has suggested that critically ill patients, treated with dexmedetomidine during nights has increased sleep efficiency and improved sleep pattern [26 27]. The quality and quantity of sleep in the critically ill patient during mechanical ventilation, can be measured accurately with polysomnography [4]. The aim of this study is to compare sleep quality and sleep pattern in critical ill patients during ICU stay after dexmedetomidine or placebo (non-sedative treatment).

Study hypotheses and endpoints

Dexmedetomidine improves deep sleep/sleep quality compared to placebo.

Method

Trial design

This study is a double blinded, randomized, controlled trial with two parallel groups (2:1 allocation ratio) comparing the effect of dexmedetomidine vs. placebo on sleep-quality in critical ill patients. The Randomized design was planned in order to equalize the groups and since a control recording were done for each patients a 2:1 allocation was feasible Fig 1.

Selection of participants

Thirty consecutive patients are planned. Inclusion site: Department of Anesthesia and Intensive care at the Hospital of Southwest Jutland, Denmark.

Inclusion criteria: admitted to the ICU. 18 years old or over. Anticipated stay at the ICU for another day after the first sleep recording. Mechanically ventilated patients. Hemodynamically stable patients. Conscious non-sedated patients with Danish language

Exclusion criteria: SOFA score above 12. Post-operative patients. Trauma patients. Patients with structural neurologic diseases (e.g., stroke, tumor), degenerative (e.g., Parkinson's disease, dementias), seizure, infections or other disorders affecting the brain based on critical history of epilepsy. Patients with a major psychiatric disorder (schizophrenia or severe depression). Patients with second- or third-degree atrioventricular block (unless pacemaker implanted). Patients of childbearing potential with positive pregnancy test or currently lactating/known pregnancy. Patients with severe agitated delirium. Patients with a high risk of death in the study period. Patients using other alpha-2 agonists (clonidine) during ICU stay. Patients with limitations in therapy. Patients participating in other studies involving use of a pharmacologically active compound. Patients otherwise unable to fulfill the study, according to investigator´s opinion.

Intervention

Recruitment procedures

Potential candidates for inclusion are selected in the ICU if they are mechanically ventilated and fulfills in- and exclusion criteria using information extracted from the hospital record information. Patients eligible for inclusion are contacted by the investigator (MD) in their room and oral/written consent are obtained with the contact nurse present.

Study treatments for both groups

Patients are screened for inclusion and oral/written consent are obtained on day one from 8.00 to 16.00. During this time baseline characteristics as presented in table 1. are obtained if the patient is eligible for inclusion. During this period the patients are prepared for PSG (polysomnography) recording thus mounted with PSG electrodes as described below. From 16.00 day one to 8.00 day two the first 16 hours PSG recordings are done. In the time frame day 2 from 8.00 - 16.00, while no recording is performed the first recording is transferred and validated by qualified staff at the Danish Center for Sleep Medicine, Rigshospitalet, Copenhagen. If the quality of the first recording is acceptable (impedance <10 KΩ, electrode placement, calibration etc.) patients are randomized,

otherwise they are excluded before randomization. Randomized patients are prepared for the second recording with an electrode check and the screener is programed to start the second recording at 16.00 day two. This recording ends at 8.00 on the third day leading to the end of the study. Dexmedetomidine/placebo are administered as described below during the second recording from 18.00 day two to 6.00 day three (fig. 2).

Study activitites	*Screening*	*Day 1 8-16.00*	*Day 1/2 16-8.00*	*Day 2 8-16.00*	*Day 2/3 16-8.00*
Inform Consent (date/Time)	x				
Inclusion critiria	x				
Exclusion Critiria	x				
Demography*	x				
Admission diagnosis	x				
Lifestile factors**	x				
Concomitant medication	x				
Analgesic medication	x				
APACHE	x				
SAPS 3	x				
SOFA	x	X		X	
Vital signs***		X	X	X	X
ECG****		X	X	X	X
RASS****					
Mobilization*****		X	X	X	X
RASS (8, 12 and 16.00)****		X		X	
CAM-ICU (8, 12 and 16.00)****		X		X	
Blod analyses †††		X		X	
Rescue medication registration††		X	X	X	X
Ventilator settings and airway management	X	X	X	X	X
Sleep evaluation			X		X
PSG †			X		X
Randomisation				X	
Treatment start					X (18.00)
Treatment stop					X (6.00)
Averse Event/SAE		X	X	X	X

Table 1. Registrations during the trail. Analgesic medication = usual analgesic medication administered during the trial. Sleep evaluation = Subjective hourly evaluation conducted by attending nurse. *Demography: Gender, ID, DoB, gender (F/M), length (cm), weight (kg) and BMI. **Lifestyles factors: smoking and alcohol ***Vital sign followed continuously: blood pressure, heart rate, body temperature, blood gases and routine safety lab values.**** done 3 times/day. ***** Mobilization is registered during the period. †PSG assessment, done twice during the study. †† Rescue medication: sedative or analgesic medication allowed or not allowed, administrated during the time period. ††† Billirubin, Carbamide and paCO2 (highest value during the period).

The attending nurse assesses subjectively if the patients are sleeping or not during the two recordings with intervals of one hour. Registration is done hourly as sleeping/not sleeping according to the state of consciousness for the majority of the hour. RASS and CAM ICU scores are done at 8.00 and 22.00 day throughout the study period.
Both study treatments are provided and delivered by Orion Pharma (Ørestads Boulevard 73, 2300 København S) to the Hospital Pharmacy. A written instruction and verbal training for dilution and blinding of the study drug were provided for the Pharmacist. The pharmacy personnel are not otherwise involved in the treatment of the patients and they are not allowed any interaction with the staff in the ICU. A log with study drug batch numbers is kept in the pharmacy.

Paracetamol and morphine are allowed for pain relief, when clinically needed and in accordance with the department's guidelines. Haloperidol and morphine areused in case of active delirium. Benzodiazepines and sedating drugs otherwise are not accepted.

Intervention group

The intervention group receives Dexmedetomidine (100µg/ml) diluted in glucose 5% to reach a concentration of 4 µg/ml. Patients are started out on continuous infusion of dexmedetomidine 0.4 µg/kg/h. In accordance with the department's guidelines the attending MD increased or decreased the infusion rate by 0.2 µg/kg/h every half hour targeting a RASS of -2. A maximum infusion rate of 1.4 µg/kg/h are allowed.

Placebo group

The placebo group are treated as the intervention groups, besides receiving glucose 5% infusion without Dexmedetomidine.

Polysomnography

Ten EEG electrodes placed on the patients scalp at the left and right frontal lobe, left and right parietal lobe and left and right occipital lobe, according to the international 10/20 system of electrode placement. Positioning is relative to the two electrodes placed on the mastoid region and the ground and reference electrode placed at the top center of the scalp. To differentiate REM sleep from NREM sleep and wakefulness, two extraocular (EOG) electrodes are placed to monitor eye movement. Two submaxillary and one chin electromyogram (EMG) electrodes are placed to

monitor muscle tone. Further two EMG electrodes are placed on the proximal lateral crus to monitor leg movement. Heartrate and oxygen saturation are recorded using two-point ECG and finger plethysmography applied on the right index finger. All data are stored by the portable screener on a SD flash card to be transferred in order to be analyzed.

The PSG is done using hardware and utensils from Somnomedics including Domino software (Somnomedics GmbH Am Sonnenstuhl 63 D-97236 Randersacker Deutschland). Calibration to ensure acceptable electrode impedance (<10 KΩ, otherwise electrodes are replaced) is conducted. Biocalibration is done prior to each PSG recording to identify pattern of eyes-open and eyes-closed, wakefulness, as well as the appearance of eye movements. Scoring of the PSG will be done according to the American Academy of Sleep Medicine guidelines (AASM).

Study Objective and endpoints

Primary objective

To investigate the effect on dexmedetomidines effect on deep sleep/sleep quality compared to placebo.

Primary endpoint

Improvement of deep sleep/sleep quality of clinical significance determined by slow wave activities.

Secondary objectives

To investigate dexmedetomidine compared with placebo's effect on a) sleep phases, b) daytime function, including anxiety and delirium,

Secondary endpoints

Sleep phases determined by PSG and daytime function including anxiety and delirium determined by Cam ICU. Alertness and wakefulness determined by RASS

Randomization method

Randomization is performed electronically in REDCap (browser based online case report form) with an allocation ratio of 2:1 for Dexmedetomidine and placebo respectively in blocks of 10 patients. The randomization numbers with corresponding allocation are stored with the REDCap data manager. The randomization codes corresponding with treatment regimen are sealed in nontransparent envelopes for the pharmacist to prepare either Dexmedetomidine or placebo. The envelope is stored with the hospital pharmacy. After preparing the medication labeling with randomization code and identification of the patient , the medication isstored in the refrigerator for the attending nurse to collect and administer.

Blinding

The treatment code is not accessible for anyone employed in the ICU, thus only the data manager, the GCP-monitor and the pharmacy personnel preparing the study drug have access to the code. Sleep assessment will be evaluated randomly by an independent doctor having only the randomization code for identification, thus blinded to the order of the recordings. A second person checked for accuracy of the blinding. The code is not broken before all data are analyzed. The data manager, who has access to the randomization code, can be contacted in case of emergency unblinding.

Trial personnel

The trial personnel are doctors and nurses in the ICU at the hospital of Southwest Jutland. The personnel are trained in non-sedation and the use of Dexmedetomidine, both in theory and by supervised practice. The hospital pharmacy personal has been trained in preparing the study and placebo drug.

Recording and reporting of SAE (Serious adverse Event)

Only SAE's that are related to the study intervention will be recorded. These events are expected to be accidental extubations and discontinuations of central venous accesses, which require reinsertion

within a few hours. Severe arterial hyper/hypotension, cardiac arrythmia or high fever related to infusion of the study drug are recorded

Investigators will report SAEs according to the national standard operational procedures. Primary investigator and the study nurses will screen for AEs (Adverse Events), which is mandatory. SAEs will be registered in the electronic case record form (REDCap) and reported to the Data Monitoring and Safety Committee (DSMC) and the Ethics Committee. The attending physician decides if an AE is serious.

Approvals, ethics and data collection

The study was approved by the Danish Ethics committee (ID:S-20180214). Registration in EudraCT (2017-001612-11DK) has been done and the trial is approved by the Danish Medicines Agency, hence monitored by the Good Clinical Practice (GCP) unit. Registration with the Danish Data Protection Agency has been done and all data collected are registered in the browser based online database REDCap, which applies with the GCP guidelines.

Sample size

Sample size evaluation were based on similar work done by Alexopoulou and Eumorfia[26], reporting significantly improved sleep efficiency (100%*TST/total PSG time) in critically ill patients when treated with dexmedetomidine. They also reported sleep architecture for stages in their crossover study. Estimates for placebo response and variation in SWS percentage of total sleep time were based on their work. Placebo is assumed to result in 0% of SWS sleep with common standard deviation of 7%. Using parallel design and assuming 10% difference in SWS time, a sample size of 12 subjects per treatment arm provide 80% power to detect statistically significant difference at 5% level using Wilcoxon-Mann-Whitney test. Using 2:1 random allocation ratio reduces power and approximately 12% more subjects are required. Randomizing a total of 30 subjects allows approximately 10% drop out rate.

Data:

Baseline equalization of the groups will be tested statically, and sleep efficiency/quality will be estimated in the two groups and compared using regression analysis after adjusting for demography, lifestyle etc. Data will be handled according to the intension to treat analysis principles. All data

will be stored in the REDCap database which complies with international Confidentiality standards. Only the investigators and the data manager will have access to the data.

Discussion

The trial investigates the potential benefit of Dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Primary investigator will by e-mail communicated the result of the study to the participants

Strength and limitation

The study is an investigator-initiated randomized placebo controlled double blinded trial, but due to the nature of the study drug, we expect in some cases that the patient's sedations level drops radically, after administration of the study drug/placebo, hence a risk of unblinding the trial.

Trial status

Inclusion has started: May 23, 2018. Completion and final analysis are expected in summer 2021. Orion Pharma have no influence on the conduct of the study and the presentation of results. Paper and PhD thesis are expected to be written and completed in 2022 and published in a peer reviewed journal.

Patient and Public Involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Conflict of interest:

The study is an investigator-initiated trial. The project receives financial and supervision support from Orion Pharma. The company is otherwise without influence on the design, interpretation of data and decision to publish the result. Mikael Sörberg is employed by Orion Pharma which has supported the project financially. The rest of the authors declare no conflict of interest.

Financial support

The study was initiated by the investigators. A grant of 70.000 Euro and the study drug was provided by Orion Corporation. The financial support was provided in part to cover the expenses of the study and the researchers have no economic interests in the company.

Author contribution

PJJ and PT developed the theory. PJJ, PT, TK, MS and JO performed computations and developed the study design. JO wrote the manuscript and all authors discussed and contributed to the final version. Financial resources were contributed by TK.

Article summery

A comparison of dexmedetomidine vs. placebo effect on sleep quality in mechanically ventilated critical ill patients: study protocol for a randomized controlled trial.

The study is an investigator-initiated randomized placebo controlled double blinded trial that evaluates the quality of sleep with PSG which is a very accurate method compared to other sleep evaluation strategies. Due to the nature of the study drug, we expect in some cases that the patient's sedations level drops radically, after administration of the study drug/placebo, hence a risk of unblinding the trial.

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Legends

Figure 1: Consort

Figure 2: Interventions during the 2-day study period

Abbreviations and definition of terms

SAE Serious Adverse Event

AASM American Asociation of Sleep Medicine

APACHE Acute Physiology and Chronic Health Evaluation

CAM-ICU Confusion Assessment Method for the ICU

CRF Case Report Form

ECG Electrocardiogram

GCP Good Clinical Practice

HR Heart Rate

ICU Intensive Care Unite

LOS Length of Stay

MV Mechanical Ventilation

NREM Non-Rapid Eye Movement sleep

PSG PolySomnoGraphy

RASS Richmonde Agitation Sedation scale

REM Rapid Eye Movement sleep

RR Respiratory Rate

SAE Serious Adverse Event

SAPS Simplified AcutePhysiologic Score

SOFA Sepsis-related organ failure assessment score

SUSAR Suspected Unexpected Serious Adverse Reaction

VT Tidal Volume

SAE Serious Adverse Even

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Figure 1

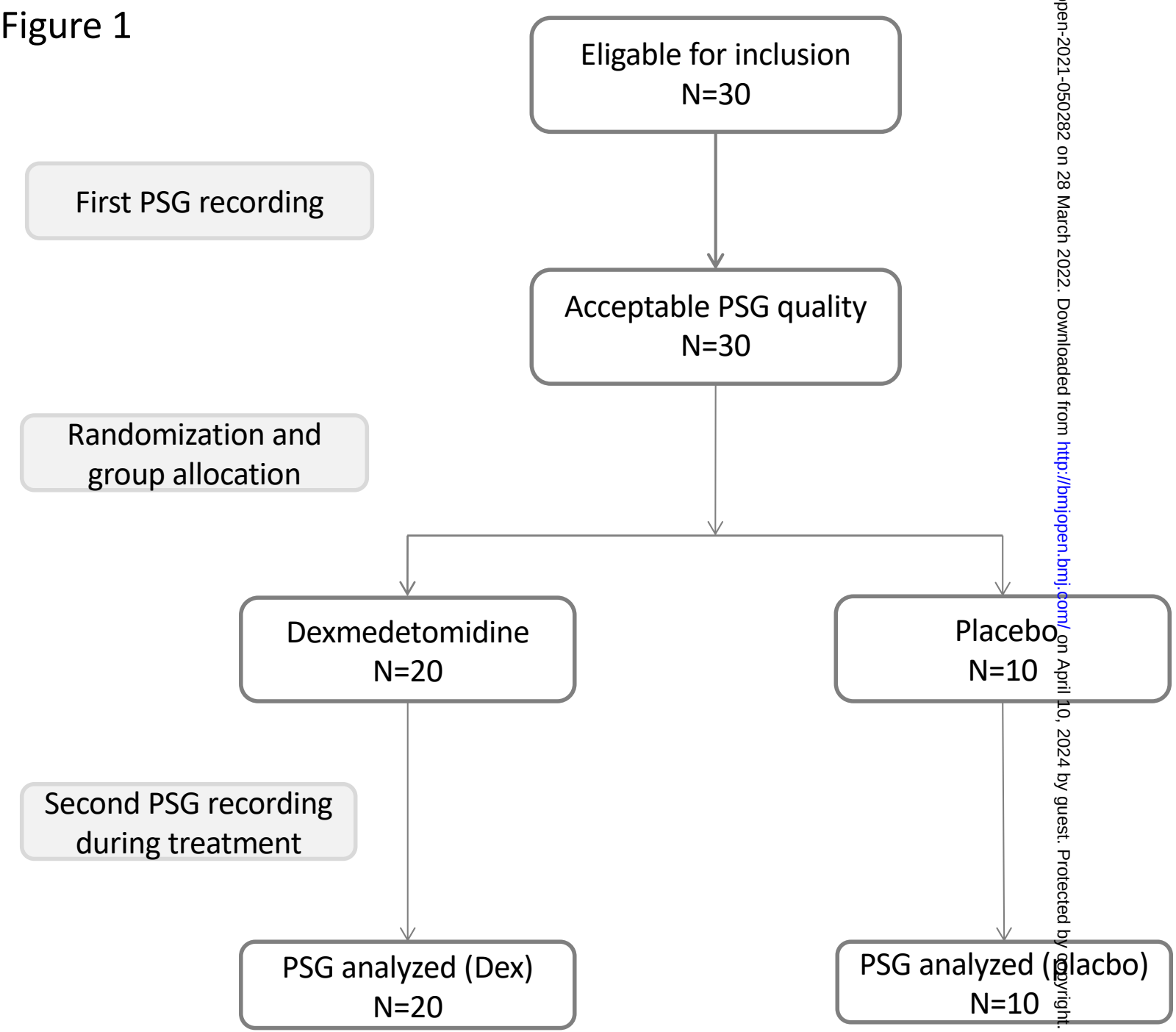
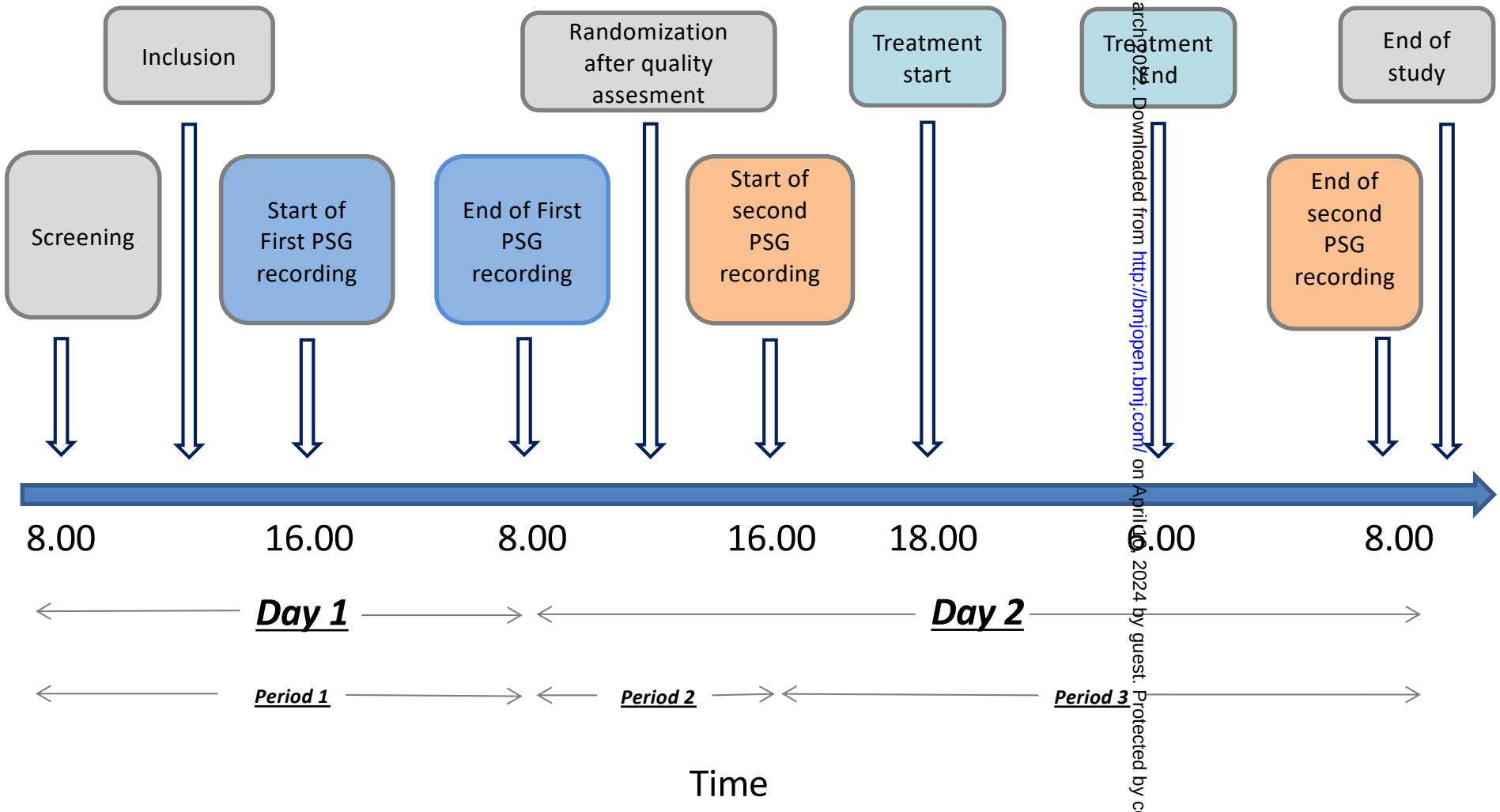


Figure 2



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
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	P9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	P9
Protocol version	#3	Date and version identifier	P1-13
Funding	#4	Sources and types of financial, material, and other support	P10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	P1
Roles and responsibilities: sponsor and funder	#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	P10
Roles and responsibilities: committees	#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)	P9
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	P3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	P3-4
Objectives	#7	Specific objectives or hypotheses	P4
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, non-inferiority, exploratory)	P3
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	P5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	P5

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P5
Interventions: modifications	#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)	P9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	P9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P6
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	P7
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)	P6
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	P9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	P5
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	P8

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	P8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P8
Methods: Data collection, management, and analysis			
Data collection plan	#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	P5-6
Data collection plan: retention	#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	P6-7,10
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	P6-7,10
Statistics: outcomes	#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	P10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P10

Statistics: analysis population and missing data	#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)	P10
Methods: Monitoring			
Data monitoring: formal committee	#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	P9
Data monitoring: interim analysis	#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	P9
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	P9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P9
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)	P9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P5,9
Consent or assent: ancillary studies	#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	P9-10

		participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P10
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	
Dissemination policy: trial results	#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	P10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	P11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	P9
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

BMJ Open

A comparison of dexmedetomidine vs. placebo effect on sleep quality in mechanically ventilated, critically ill patients: Study protocol for a randomised controlled trial

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A COMPARISON OF DEXMEDETOMIDINE vs. PLACEBO EFFECT ON SLEEP-QUALLITY IN MECHANICALLY VENTILATED CRITICALLY ILL PATIENTS: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

Keyword: Dexmedetomidine, Polysomnography, Critically ill, Sleep-quality,

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Abstract:

Introduction: Sleep deprivation, which is a common complication in the ICU, is associated with delirium and increased mortality. Sedation with GABA agonists (propofol, benzodiazepam) results in significant disturbance of the sleep architecture. Dexmedetomidine is a lipophilic imidazole with an affinity for α_2-adrenoceptors and it has sedative and analgesic properties. It has been reported to enhance sleep efficiency, thus sedate while preserving sleep architecture.

Methods and analysis: Thirty consecutive patients are planned to be included, at the department of Anesthesia and Intensive care at the Hospital of Southwest Jutland, Denmark. The study is a double blinded, randomized, controlled trial with two parallel groups (2:1 allocation ratio).
Screening and inclusion will be done on day one from 8.00 to 16.00. Two 16 hours PSG (polysomnography) recording will be done starting at 16.00 on day one and day two.
Randomization is performed if the first recording is of acceptable quality, otherwise the patient is excluded before randomization. Dexmedetomidine/placebo will be administered during the second recording from 18.00 day two to 6.00 day three. **Primary endpoint:** Improvement of sleep quality of clinical significance determined by PSG. **Secondary endpoints:** Sleep phases determined by PSG. Daytime function and delirium determined by Cam ICU. Alertness and wakefulness determined by RASS. The objective is to compare the effect of dexmedetomidine vs. placebo on sleep-quality in critical ill mechanically ventilated patients.

Ethics and dissemination: The trial investigate the potential benefit of Dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Publication in peer reviewed journal are planned and the study has been approved by the Danish Ethics Committee (ID:S-20180214).

Strength and limitations of this study:

- Investigator-initiated randomized placebo controlled, double blinded trial.
- Sleep evaluation by polysomnography.
- Inclusion of consecutive patients.
- Due to study drug nature (sedative), blinding will in some cases be challenging.

Introduction:

Sleep disturbance in mechanically ventilated critically ill patients is a common complication [1-4]. About 50 percent of ICU patients report disturbed sleep and one-third continues to suffer from poor sleep quality 6-12 months after discharge [5]. Patients reports sleep-wake disorganization, sleep fragmentation and abnormal sleep architecture with increased stage 1 and stage 2 non-rapid eye movement (NREM) sleep, decreased stage 3 (slow wave sleep (SWS)) and rapid eye movement (REM) sleep [1-4]. Sleep deprivation is associated with dysfunction of the immune and cardiovascular systems, disturbed metabolism, impaired memory, delirium, and in turn increased mortality [6-8]. Sedatives and analgesics are often administered to the critically ill patient to increase comfort, decrease anxiety, and promote sleep. There are two commonly used classes of sedatives: benzodiazepine and propofol interacting with the gamma-aminobutyric acid (GABA) receptor and those with an affinity for alpha-2 receptors in the locus coeruleus, such as dexmedetomidine [2]. Infusing propofol and midazolam induce sleep and the perception of sleeping [4 9], however sedation with GABA agonists results in significant disturbance of sleep architecture, including suppression of SWS and REM sleep [1-4]. Administration of GABA agonists, especially benzodiazepine, has been reported to cause delirium, prolong mechanical ventilation and ICU stay [7 10]. For several years the standard practice for sedation of patients in need of mechanical ventilation has been a combination of opioids and intravenous infusion of benzodiazepines and/or propofol. This strategy is known to prolong MV, weaning from the ventilator and LOS in ICU and hospital [11 12]. Recent guidelines [13 14] have advocated a revision of ICU sedation practices towards optimal patient comfort with minimal sedation [14] to improve clinical outcomes in mechanically ventilated adult ICU patients. As a result light or non-sedation has been applied to avoid affecting sleep architecture and delirium and previous data demonstrate that comfort during mecanical ventilation (MV) can be achieved with no or very light sedation, which is associated with lower incidences of delirium and shorter Lengh of Stay (LOS) in ICU [15-18].

Dexmedetomidine is a lipophilic imidazole derivative with an affinity for α_2-adrenoceptors 1600 times higher than for α_1-adrenoceptors and 8 times higher than the prototype α_2 agonist drug, clonidine [19]. It has sedative and analgesic properties and can be used as an alternative in cases where non-sedation is not applicable. It has been reported to inhibit the release of norepinephrine in

the locus coeruleus as well as enhancement of SWS by mimicking the endogenous NREM sleep pathway [20]. Dexmedetomidine activates central pre- and postsynaptic α_2-receptors in the locus coeruleus, thereby inducing a state of unconsciousness similar to natural sleep – resembling NREM sleep [21]. The action involves an inhibition of the reticular activation system primarily involving cortex but to lesser degree cardio-pulmonary function. This unique site of action lends Dexmedetomidine an equally unique sedative profile, conferring ability to sedate while at the same time allowing for patient arousability and interaction with relatives and staff. As a sedative, Dexmedetomidine is notable for its lack of respiratory drive suppression [22].

The minimal sedation strategy has among other conditions revealed sleep disturbances especially during night time. Dexmedetomidine, has been shown to provide good comfort during MV with a good safety profile [23-25] and reduced time to extubation [12]. In addition previous studies has suggested that critically ill patients, treated with dexmedetomidine during nights has increased sleep efficiency and improved sleep pattern [26 27]. The quality and quantity of sleep in the critically ill patient during mechanical ventilation, can be measured accurately with polysomnography [4]. The aim of this study is to compare sleep quality and sleep pattern in critical ill patients during ICU stay after dexmedetomidine or placebo (non-sedative treatment).

Study hypotheses and endpoints

Dexmedetomidine improves deep sleep/sleep quality compared to placebo.

Method

Trial design

This study is a double blinded, randomized, controlled trial with two parallel groups (2:1 allocation ratio) comparing the effect of dexmedetomidine vs. placebo on sleep-quality in critical ill patients. The Randomized design was planned in order to equalize the groups and since a control recording were done for each patients a 2:1 allocation was feasible (Fig 1.).

Patient and Public Involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Selection of participants

Thirty consecutive patients are planned. Inclusion site: Department of Anesthesia and Intensive care at the Hospital of Southwest Jutland, Denmark.

Inclusion criteria: admitted to the ICU. 18 years old or over. Anticipated stay at the ICU for another day after the first sleep recording. Mechanically ventilated patients. Hemodynamically stable patients. Conscious non-sedated patients with Danish language

Exclusion criteria: SOFA score above 12. Post-operative patients. Trauma patients. Patients with structural neurologic diseases (e.g., stroke, tumor), degenerative (e.g., Parkinson's disease, dementias), seizure, infections or other disorders affecting the brain based on critical history of epilepsy. Patients with a known psychiatric disorder (e.g., schizophrenia, severe depression). Patients with second- or third-degree atrioventricular block (unless pacemaker implanted). Patients of childbearing potential with positive pregnancy test or currently lactating/known pregnancy. Patients with severe agitated delirium. Patients with a high risk of death in the study period. Patients using other alpha-2 agonists (clonidine) during ICU stay. Patients with limitations in therapy (e.g. resuscitation, dialysis). Patients participating in other studies involving use of a pharmacologically active compound. Patients otherwise unable to fulfill the study, according to investigator´s opinion.

Intervention

Recruitment procedures

Potential candidates for inclusion are selected in the ICU if they are mechanically ventilated and fulfills in- and exclusion criteria using information extracted from the hospital record information. Patients eligible for inclusion are contacted by the investigator (MD) in their room and oral/written consent are obtained with the contact nurse present.

Study treatments for both groups

Patients are screened for inclusion and oral/written consent are obtained on day one from 8.00 to 16.00. During this time baseline characteristics as presented in (Table 1.). are obtained if the patient is eligible for inclusion. During this period the patients are prepared for PSG (polysomnography) recording, thus mounted with PSG electrodes as described below. From 16.00 day one to 8.00 day

two the first 16 hours PSG recordings are done. In the time frame day 2 from 8.00 - 16.00, while no recording is performed the first recording is transferred and validated by qualified staff at the Danish Center for Sleep Medicine, Rigshospitalet, Copenhagen. If the quality of the first recording is acceptable (impedance <10 KΩ, electrode placement, calibration etc.) patients are randomized, otherwise they are excluded before randomization. Randomized patients are prepared for the second recording with an electrode check and the PSG screener is programed to start the second recording at 16.00 day two. This recording ends at 8.00 on the third day leading to the end of the study. Dexmedetomidine/placebo will be administered as described below during the second recording from 18.00 day two to 6.00 day three (Fig. 2).

Study activitites	*Screening*	*Day 1 8-16.00*	*Day 1/2 16-8.00*	*Day 2 8-16.00*	*Day 2/3 16-8.00*
Inform Consent (date/Time)	x				
Inclusion critiria	x				
Exclusion Critiria	x				
Demography*	x				
Admission diagnosis	x				
Lifestile factors**	x				
Concomitant medication	x				
Analgesic medication	x				
APACHE	x				
SAPS 3	x				
SOFA	x	X		X	
Vital signs***		X	X	X	X
ECG****		X	X	X	X
RASS continuously (18-8.00)			X		X
Mobilization*****		X	X	X	X
RASS (8, 12 and 16.00)****		X		X	
CAM-ICU (8, 12 and 16.00)****		X		X	
Blod analyses †††		X		X	
Rescue medication registration††		X	X	X	X
Ventilator settings and airway management	X	X	X	X	X
Sleep evaluation			X		X
PSG †			X		X
Randomisation				X	
Treatment start					X (18.00)
Treatment stop					X (6.00)
Averse Event/SAE		X	X	X	X

Table 1. Registrations during the trail. Analgesic medication = usual analgesic medication administered during the trial. Sleep evaluation = Subjective hourly evaluation conducted by attending nurse. *Demography: Gender, ID, DoB, gender (F/M), length (cm), weight (kg) and BMI. **Lifestyles factors: smoking and alcohol ***Vital sign followed

continuously: blood pressure, heart rate, body temperature, blood gases and routine safety lab values.**** done 3 times/day. ***** Mobilization is registered during the period. †PSG assessment, done twice during the study. †† Rescue medication: sedative or analgesic medication allowed or not allowed, administrated during the time period. ††† Billirubin, Carbamide and paCO2 (highest value during the period).

The attending nurse assesses subjectively if the patients are sleeping or not during the two recordings with intervals of one hour. Registration is done hourly as sleeping/not sleeping according to the state of consciousness for the majority of the hour. RASS and CAM ICU scores are done at 8.00 and 22.00 day throughout the study period.

Both study treatments are provided and delivered by Orion Pharma (Ørestads Boulevard 73, 2300 København S) to the Hospital Pharmacy. A written instruction and verbal training for dilution and blinding of the study drug were provided for the Pharmacist. The pharmacy personnel are not otherwise involved in the treatment of the patients, and they are not allowed any interaction with the staff in the ICU. A log with study drug batch numbers is kept in the pharmacy.

Paracetamol and morphine are allowed for pain relief, when clinically needed and in accordance with the department's guidelines. Haloperidol and morphine areused in case of active delirium. Benzodiazepines and sedating drugs otherwise are not accepted.

Intervention group

The intervention group receives Dexmedetomidine (100µg/ml) diluted in glucose 5% to reach a concentration of 4 µg/ml. Patients are started out on continuous infusion of dexmedetomidine 0.4 µg/kg/h. In accordance with the department's guidelines the attending MD increased or decreased the infusion rate by 0.2 µg/kg/h every half hour targeting a RASS of -2. A maximum infusion rate of 1.4 µg/kg/h are allowed.

Placebo group

The placebo group are treated as the intervention groups, besides receiving glucose 5% infusion without Dexmedetomidine.

Polysomnography

Ten EEG electrodes placed on the patients scalp at the left and right frontal lobe, left and right parietal lobe and left and right occipital lobe, according to the international 10/20 system of electrode placement. Positioning is relative to the two electrodes placed on the mastoid region and the ground and reference electrode placed at the top center of the scalp. To differentiate REM sleep from NREM sleep and wakefulness, two extraocular (EOG) electrodes are placed to monitor eye movement. Two submaxillary and one chin electromyogram (EMG) electrodes are placed to monitor muscle tone. Further two EMG electrodes are placed on the proximal lateral crus to monitor leg movement. Heartrate and oxygen saturation are recorded using two-point ECG and finger plethysmography applied on the right index finger. All data are stored by the portable screener on a SD flash card to be transferred in order to be analyzed.

The PSG is done using hardware and utensils from Somnomedics including Domino software (Somnomedics GmbH Am Sonnenstuhl 63 D-97236 Randersacker Deutschland). Calibration to ensure acceptable electrode impedance (<10 KΩ, otherwise electrodes are replaced) is conducted. Biocalibration is done prior to each PSG recording to identify pattern of eyes-open and eyes-closed, wakefulness, as well as the appearance of eye movements. Scoring of the PSG will be done according to the American Academy of Sleep Medicine guidelines (AASM).

Study Objective and endpoints

Primary objective

To investigate the effect on dexmedetomidines effect on deep sleep/sleep quality compared to placebo.

Primary endpoint

Improvement of deep sleep/sleep quality of clinical significance determined by sleep efficiency activities.

Secondary objectives

To investigate dexmedetomidine compared with placebo's effect on a) sleep phases, b) daytime function and delirium.

Secondary endpoints

Sleep phases determined by PSG and daytime function and delirium determined by CAM ICU. Alertness and wakefulness determined by RASS

Randomization method

Randomization is performed electronically in REDCap (browser based online case report form) with an allocation ratio of 2:1 for Dexmedetomidine and placebo respectively in blocks of 10 patients. The randomization numbers with corresponding allocation are stored with the REDCap data manager. The randomization codes corresponding with treatment regimen are sealed in nontransparent envelopes for the pharmacist to prepare either Dexmedetomidine or placebo. The envelope is stored with the hospital pharmacy. After preparing the medication labeling with randomization code and identification of the patient, the medication will be stored in the refrigerator for the attending nurse to collect and administer.

Blinding

The treatment code is not accessible for anyone employed in the ICU, thus only the data manager, the GCP-monitor and the pharmacy personnel preparing the study drug have access to the code. Sleep assessment will be evaluated randomly by an independent doctor having only the randomization code for identification, thus blinded to the order of the recordings. A second person checks for accuracy of the blinding. The code is not broken before all data are analyzed. The data manager, who has access to the randomization code, can be contacted in case of emergency unblinding.

Trial personnel

The trial personnel are doctors and nurses in the ICU at the hospital of Southwest Jutland. The personnel are trained in non-sedation and the use of Dexmedetomidine, both in theory and by supervised practice. The hospital pharmacy personal has been trained in preparing the study and placebo drug.

Recording and reporting of SAE (Serious adverse Event)

Only SAE's that are related to the study intervention will be recorded. These events are expected to be accidental extubation and discontinuations of central venous accesses, which require reinsertion within a few hours. Severe arterial hyper/hypotension, cardiac arrythmia or high fever related to infusion of the study drug are recorded

Investigators will report SAEs according to the national standard operational procedures. Primary investigator and the study nurses will screen for AEs (Adverse Events), which is mandatory. SAEs will be registered in the electronic case record form (REDCap) and reported to the Data Monitoring and Safety Committee (DSMC) and the Ethics Committee. The attending physician decides if an AE is serious.

Approvals, ethics, dissemination, and data collection

The study was approved by the Danish Ethics committee (ID:S-20180214). Registration in EudraCT (2017-001612-11DK) has been done and the trial is approved by the Danish Medicines Agency, hence monitored by the Good Clinical Practice (GCP) unit. Registration with the Danish Data Protection Agency has been done and all data collected are registered in the browser based online database REDCap, which applies with the GCP guidelines. Publication in peer reviewed journal has been planned.

Sample size

Sample size evaluation were based on similar work done by Alexopoulou and Eumorfia[26], reporting significantly improved sleep efficiency (100%*TST/total PSG time) in critically ill patients when treated with dexmedetomidine. They also reported sleep architecture for stages in their crossover study. Estimates for placebo response and variation in SWS percentage of total sleep time were based on their work. Placebo is assumed to result in 0% of SWS sleep with common standard deviation of 7%. Using parallel design and assuming 10% difference in SWS time, a sample size of

12 subjects per treatment arm provide 80% power to detect statistically significant difference at 5% level using Wilcoxon-Mann-Whitney test. Using 2:1 random allocation ratio reduces power and approximately 12% more subjects are required. Randomizing a total of 30 subjects allows approximately 10% drop out rate.

Data:

Baseline equalization of the groups will be tested statically, and sleep efficiency/quality will be estimated in the two groups and compared using ttest/rank sum according to the nature of the data. Adjustment for baseline characteristics will be performed using regression analysis. Data will be handled according to the intension to treat analysis principles. All data will be stored in the REDCap database which complies with international Confidentiality standards. Only the investigators and the data manager will have access to the data.

Two reports will be generated regarding the sleep data one using data the time frame 22 to 8.00 and one using data from 18 to 6.00.

Discussion

The trial investigates the potential benefit of Dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Primary investigator will by e-mail communicated the result of the study to the participants.

In the ICU one aims to restore normal circadian rhythm for non-sedated, non-delirious patients, hence mobilized and encouraged to stay awake during the day (8-22:00). At night Pharmacologic and non-pharmacologic measures are done for the patient to be sleeping. If the patient on the other hand present delirious symptoms, sleep induction might be necessary, even if it does not complie with a normal circadian rhythm in order to break a vicious circle. Hence the study report will contain sleep patterns for both sedation strategies (22 to 8.00 and 18 to 6.00).

Recording during two consecutive days has been planned as opposed to two days apart. Thus, the patient will exhibit the same degree of critical illness and encephalopathic state.

Trial status

Inclusion has started: May 23, 2018. Completion and final analysis are expected in summer 2021. Orion Pharma have no influence on the conduct of the study and the presentation of results. Paper

and PhD thesis are expected to be written and completed in 2022 and published in a peer reviewed journal.

Competing interests:

The project receives financial and supervision support from Orion Pharma. The company is otherwise without influence on the design, interpretation of data and decision to publish the result. Mikael Sörberg is employed by Orion Pharma which has supported the project financially. The rest of the authors declare no competing of interest.

Funding Statement

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Author contribution

PJJ and PT developed the theory. PJJ, PT, TK, MS and JO performed computations and developed the study design. JO wrote the manuscript and all authors discussed and contributed to the final version. Financial resources were contributed by TK.

Acknowledgement:

Toni Sarapohja, Senior Principal Biostatistician, Orion Corporation is acknowledged for statistical support.

Legends

Figure 1: Consort

Figure 2: Interventions during the 2-day study period

Abbreviations and definition of terms

SAE Serious Adverse Event

AASM American Asociation of Sleep Medicine

APACHE Acute Physiology and Chronic Health Evaluation

CAM-ICU Confusion Assessment Method for the ICU

CRF Case Report Form

ECG Electrocardiogram

GCP Good Clinical Practice

HR Heart Rate

ICU Intensive Care Unite

LOS Length of Stay

MV Mechanical Ventilation

NREM Non-Rapid Eye Movement sleep

PSG PolySomnoGraphy

RASS Richmonde Agitation Sedation scale

REM Rapid Eye Movement sleep

RR Respiratory Rate

SAE Serious Adverse Event

SAPS Simplified AcutePhysiologic Score

SOFA Sepsis-related organ failure assessment score

SUSAR Suspected Unexpected Serious Adverse Reaction

VT Tidal Volume

SAE Serious Adverse Even

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Figure 1

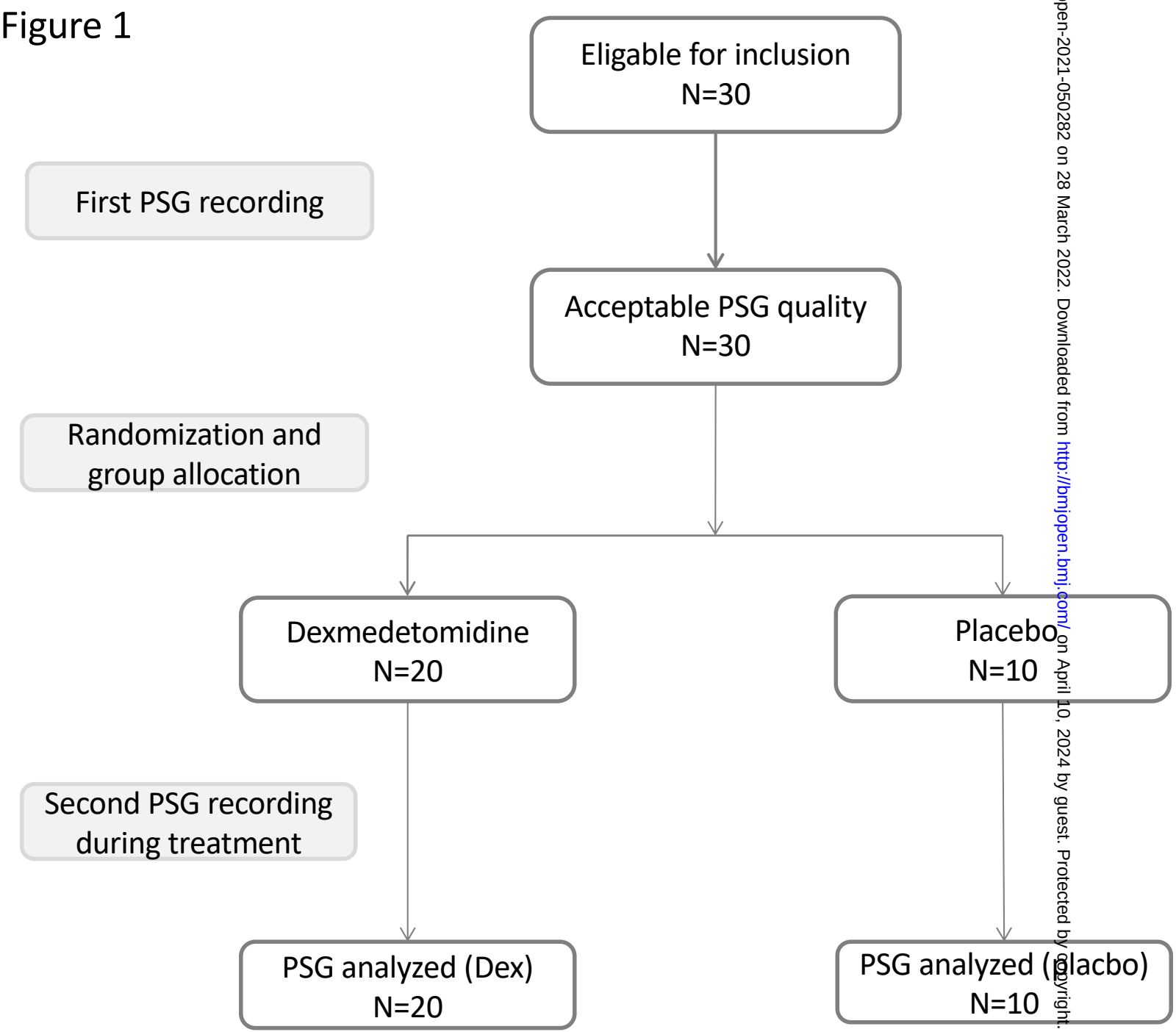
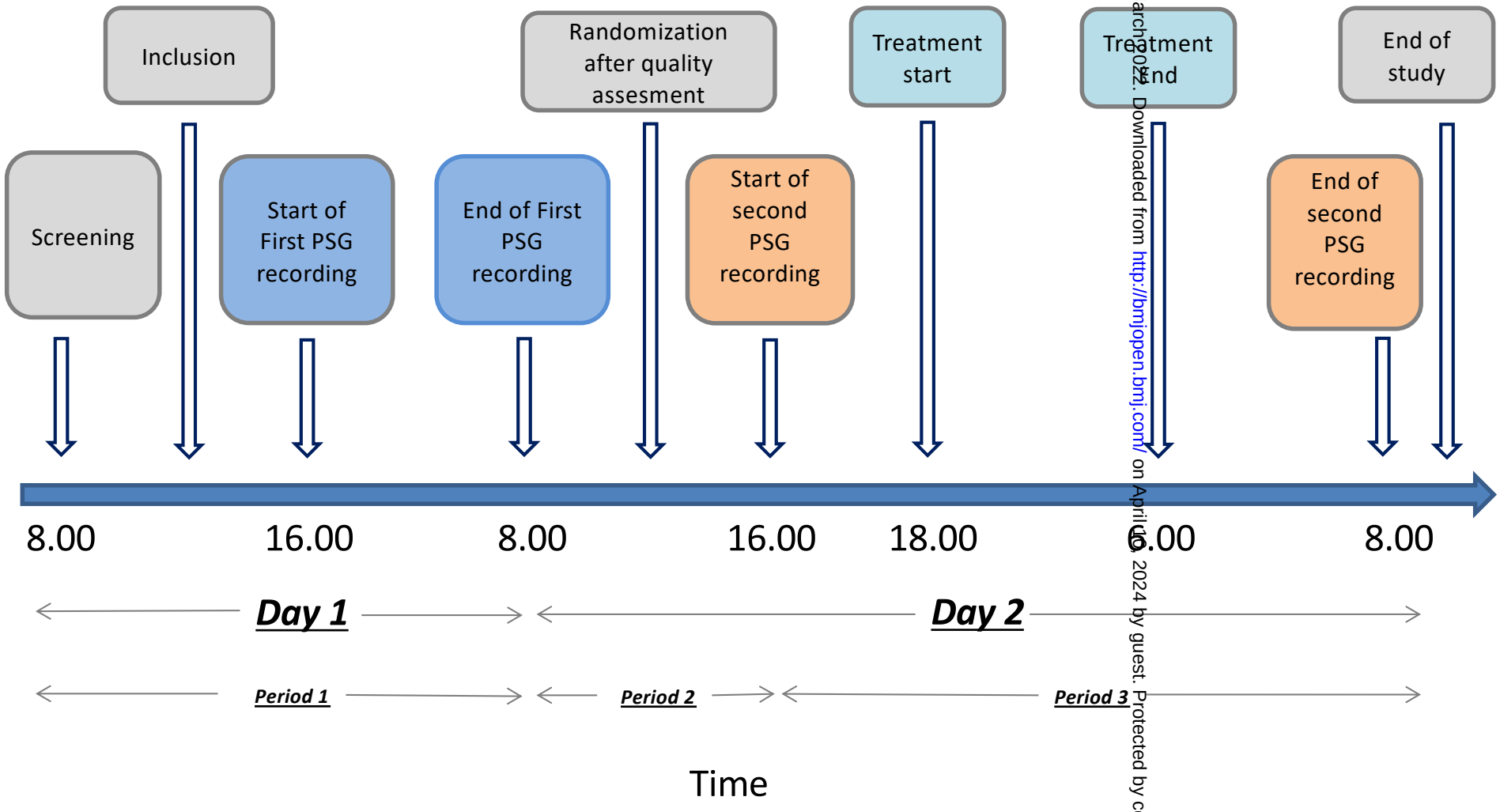


Figure 2



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
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	P9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	P9
Protocol version	#3	Date and version identifier	P1-13
Funding	#4	Sources and types of financial, material, and other support	P10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	P1
Roles and responsibilities: sponsor and funder	#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	P10
Roles and responsibilities: committees	#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)	P9
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	P3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	P3-4
Objectives	#7	Specific objectives or hypotheses	P4
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, non-inferiority, exploratory)	P3
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	P5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	P5

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P5
Interventions: modifications	#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)	P9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	P9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P6
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	P7
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)	P6
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	P9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	P5
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	P8

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	P8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P8
Methods: Data collection, management, and analysis			
Data collection plan	#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	P5-6
Data collection plan: retention	#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	P6-7,10
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	P6-7,10
Statistics: outcomes	#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	P10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P10

Statistics: analysis population and missing data	#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)	P10
Methods: Monitoring			
Data monitoring: formal committee	#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	P9
Data monitoring: interim analysis	#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	P9
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	P9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P9
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)	P9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P5,9
Consent or assent: ancillary studies	#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	P9-10

		participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P10
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	
Dissemination policy: trial results	#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	P10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	P11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	P9
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

BMJ Open

A COMPARISON OF DEXMEDETOMIDINE vs. PLACEBO EFFECT ON SLEEP QUALITY IN MECHANICALLY VENTILATED CRITICALLY ILL PATIENTS: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

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A COMPARISON OF DEXMEDETOMIDINE vs. PLACEBO EFFECT ON SLEEP QUALITY IN MECHANICALLY VENTILATED CRITICALLY ILL PATIENTS: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

Keyword: Dexmedetomidine, Polysomnography, Critically ill, Sleep-quality,

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Abstract:

Introduction: Sleep deprivation, which is a common complication in the ICU, is associated with delirium and increased mortality. Sedation with GABA agonists (propofol, benzodiazepine) results in significant disturbance of the sleep architecture. Dexmedetomidine is a lipophilic imidazole with an affinity for α_2-adrenoceptors and it has sedative and analgesic properties. It has been reported to enhance sleep efficiency, thus sedate while preserving sleep architecture.

Methods and analysis: Thirty consecutive patients are planned to be included, at the department of Anesthesia and Intensive care at the Hospital of Southwest Jutland, Denmark. The study is a double blinded, randomized, controlled trial with two parallel groups (2:1 allocation ratio).
Screening and inclusion will be done on day one from 8.00 to 16.00. Two 16 hours PSG (polysomnography) recording will be done starting at 16.00 on day one and day two.
Randomization is performed if the first recording is of acceptable quality, otherwise the patient is excluded before randomization. Dexmedetomidine/placebo will be administered during the second recording from 18.00 day two to 6.00 day three. **Primary endpoint:** Improvement of sleep quality of clinical significance determined by PSG. **Secondary endpoints:** Sleep phases determined by PSG. Daytime function and delirium determined by CAM-ICU. Alertness and wakefulness determined by RASS. The objective is to compare the effect of dexmedetomidine vs. placebo on sleep-quality in critical ill mechanically ventilated patients.

Ethics and dissemination: The trial investigate the potential benefit of Dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Publication in peer reviewed journal are planned and the study has been approved by the National Committee on Health Research Ethics (ID:S-20180214).

Strength and limitations of this study:

- Investigator-initiated randomized placebo controlled, double blinded trial.
- Sleep evaluation by polysomnography.
- Inclusion of consecutive patients.
- Due to study drug nature (sedative), blinding will in some cases be challenging.

Introduction:

Sleep disturbance in mechanically ventilated critically ill patients is a common complication [1-4]. About 50 percent of ICU patients report disturbed sleep and one-third continues to suffer from poor sleep quality 6-12 months after discharge [5]. Patients report sleep-wake disorganization, sleep fragmentation and abnormal sleep architecture with increased stage 1 and 2 non-rapid eye movement (NREM) sleep, decreased stage 3 (slow wave sleep (SWS)) and rapid eye movement (REM) sleep [1-4]. Sleep deprivation is associated with dysfunction of the immune and cardiovascular systems, disturbed metabolism, impaired memory, delirium, and in turn increased mortality [6-8]. Sedatives and analgesics are often administered to increase comfort, decrease anxiety, and promote sleep. There are two commonly used classes of sedatives: 1) Benzodiazepine and propofol interacting with the gamma-aminobutyric acid (GABA) receptor 2) Sedatives with an affinity for alpha-2 receptors in the locus coeruleus, such as dexmedetomidine [2]. Infusing propofol and midazolam induce sleep and the perception of sleeping [4 9], however sedation with GABA agonists results in significant disturbance of sleep architecture, including suppression of SWS and REM sleep [1-4]. Administration of GABA agonists, especially benzodiazepine, has been reported to cause delirium, prolong mechanical ventilation and ICU stay [7 10]. For several years the standard practice for sedation of patients in need of mechanical ventilation has been a combination of opioids and intravenous infusion of benzodiazepine and/or propofol. This strategy is known to prolong MV, weaning from the ventilator and LOS in ICU and hospital [11 12]. Recent guidelines [13 14] have advocated a revision of ICU sedation practices towards optimal patient comfort with minimal sedation [13] to improve clinical outcomes in mechanically ventilated adult ICU patients. As a result light or non-sedation has been applied to avoid affecting sleep architecture and previous data demonstrate that comfort during mecanical ventilation (MV) can be achieved with no or very light sedation. Dexmedetomidine or light sedation has been shown to lower the incidences of delirium, when comparing with placebo or standard regimen, however when comparing propofol vs. dexmedetomidine in critically ill sepsis patients, delirium insidense has not been shown to differ[15-20].

Dexmedetomidine is a lipophilic imidazole derivative with an affinity for α_2-adrenoceptors 1600 times higher than for α_1-adrenoceptors and 8 times higher than the prototype α_2 agonist drug,

clonidine [21]. It has sedative and analgesic properties and can be used as an alternative in cases where non-sedation is not applicable. It has been reported to inhibit the release of norepinephrine in the locus coeruleus as well as enhancement of SWS by mimicking the endogenous NREM sleep pathway [22]. Dexmedetomidine activates central pre- and postsynaptic α_2-receptors in the locus coeruleus, thereby inducing a state of unconsciousness similar to natural sleep – resembling NREM sleep [23]. The action involves an inhibition of the reticular activation system primarily involving cortex but to lesser degree cardio-pulmonary function. This unique site of action lends Dexmedetomidine an equally unique sedative profile, conferring ability to sedate while at the same time allowing for patient arousability and interaction with relatives and staff. As a sedative, Dexmedetomidine is notable for its lack of respiratory drive suppression [24].

The minimal sedation strategy has among other conditions revealed sleep disturbances especially during night time. Dexmedetomidine, has been shown to provide good comfort during MV with a good safety profile [25-27] and reduced time to extubation [12]. In addition previous studies has suggested that critically ill patients, treated with dexmedetomidine during nights has increased sleep efficiency and improved sleep pattern [28 29]. The quality and quantity of sleep in the critically ill patient during mechanical ventilation, can be measured accurately with polysomnography [4]. The aim of this study is to compare sleep quality and sleep pattern in critical ill patients during ICU stay after dexmedetomidine or placebo (non-sedative treatment).

Study hypotheses and endpoints

Dexmedetomidine improves deep sleep/sleep quality compared to placebo.

Method

Trial design

This study is a double blinded, randomized, controlled trial with two parallel groups (2:1 allocation ratio) comparing the effect of dexmedetomidine vs. placebo on sleep-quality in critical ill patients. The Randomized design was planned to equalize the groups and since a control recording were done for each patients a 2:1 allocation was feasible (Fig 1.).

Patient and Public Involvement statement

Patients or the public are not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Selection of participants

Thirty consecutive patients are planned. Inclusion site: Department of Anesthesia and Intensive care at the Hospital of Southwest Jutland, Denmark.

Inclusion criteria: admitted to the ICU. 18 years old or over. Anticipated stay at the ICU for another day after the first sleep recording. Mechanically ventilated patients. Hemodynamically stable patients. Conscious non-sedated patients with Danish language

Exclusion criteria: SOFA score above 12. Post-operative patients. Trauma patients. Patients with structural neurologic diseases (e.g., stroke, tumor), degenerative (e.g., Parkinson's disease, dementias), seizure, infections or other disorders affecting the brain based on critical history of epilepsy. Patients with a known psychiatric disorder (e.g., schizophrenia, severe depression). Patients with second- or third-degree atrioventricular block (unless pacemaker implanted). Patients of childbearing potential with positive pregnancy test or currently lactating/known pregnancy. Patients with severe agitated delirium. Patients with a high risk of death in the study period. Patients using other alpha-2 agonists (clonidine) during ICU stay. Patients with limitations in therapy (e.g. resuscitation, dialysis). Patients participating in other studies involving use of a pharmacologically active compound. Patients otherwise unable to fulfill the study, according to investigator´s opinion.

Intervention

Recruitment procedures

Potential candidates for inclusion are selected in the ICU if they are mechanically ventilated and fulfills in- and exclusion criteria using information extracted from the hospital record information. Patients eligible for inclusion are contacted by the investigator (MD) in their room and oral/written consent are obtained with the contact nurse present.

Study treatments for both groups

Patients are screened for inclusion and oral/written consent are obtained on day one from 8.00 to 16.00. During this time baseline characteristics as presented in (Table 1.). are obtained if the patient is eligible for inclusion. During this period the patients are prepared for PSG (polysomnography) recording, thus mounted with PSG electrodes as described below. From 16.00 day one to 8.00 day two the first 16 hours PSG recordings are done. In the time frame day 2 from 8.00 - 16.00, while no recording is performed the first recording is transferred and validated by qualified staff at the Danish Center for Sleep Medicine, Rigshospitalet, Copenhagen. If the quality of the first recording is acceptable (impedance <10 KΩ, electrode placement, calibration etc.) patients are randomized, otherwise they are excluded before randomization. Randomized patients are prepared for the second recording with an electrode check and the PSG screener is programed to start the second recording at 16.00 day two. This recording ends at 8.00 on the third day leading to the end of the study. Dexmedetomidine/placebo will be administered as described below during the second recording from 18.00 day two to 6.00 day three (Fig. 2).

Study activitites	*Screening*	*Day 1 8-16.00*	*Day 1/2 16-8.00*	*Day 2 8-16.00*	*Day 2/3 16-8.00*
Inform Consent (date/Time)	x				
Inclusion critiria	x				
Exclusion Critiria	x				
Demography*	x				
Admission diagnosis	x				
Lifestile factors**	x				
Concomitant medication	x				
Analgesic medication	x				
APACHE	x				
SAPS 3	x				
SOFA	x	X		X	
Vital signs***		X	X	X	X
ECG****		X	X	X	X
RASS continuously (18-8.00)			X		X
Mobilization*****		X	X	X	X
RASS (8, 12 and 16.00)****		X		X	
CAM-ICU (8, 12 and 16.00)****		X		X	
Blod analyses †††		X		X	
Rescue medication registration††		X	X	X	X
Ventilator settings and airway management	X	X	X	X	X
Sleep evaluation			X		X
PSG †			X		X
Randomisation				X	
Treatment start					X (18.00)

Treatment stop					X (6.00)
Averse Event/SAE		X	X	X	X

Table 1. Registrations during the trail. Analgesic medication = usual analgesic medication administered during the trial. Sleep evaluation = Subjective hourly evaluation conducted by attending nurse. *Demography: Gender, ID, DoB, gender (F/M), length (cm), weight (kg) and BMI. **Lifestyles factors: smoking and alcohol ***Vital sign followed continuously: blood pressure, heart rate, body temperature, blood gases and routine safety lab values.**** done 3 times/day. ***** Mobilization is registered during the period. †PSG assessment, done twice during the study. †† Rescue medication: sedative or analgesic medication allowed or not allowed, administrated during the time period. ††† Billirubin, Carbamide and paCO2 (highest value during the period).

The attending nurse assesses subjectively if the patients are sleeping or not during the two recordings with intervals of one hour. Registration is done hourly as sleeping/not sleeping according to the state of consciousness for the majority of the hour. RASS and CAM ICU scores are done at 8.00 and 22.00 day throughout the study period.

Both study treatments are provided and delivered by Orion Pharma (Ørestads Boulevard 73, 2300 København S) to the Hospital Pharmacy. A written instruction and verbal training for dilution and blinding of the study drug were provided for the Pharmacist. The pharmacy personnel are not otherwise involved in the treatment of the patients, and they are not allowed any interaction with the staff in the ICU. A log with study drug batch numbers is kept in the pharmacy.

Paracetamol and morphine are allowed for pain relief, when clinically needed and in accordance with the department's guidelines. Haloperidol and morphine are used in case of active delirium. Benzodiazepines and sedating drugs otherwise are not accepted, and the patients will be excluded if administered.

Intervention group

The intervention group receives Dexmedetomidine (100µg/ml) diluted in glucose 5% to reach a concentration of 4 µg/ml. Patients are started out on continuous infusion of dexmedetomidine 0.4 µg/kg/h. In accordance with the department's guidelines the attending physician increases or decreases the infusion rate by 0.2 µg/kg/h every half hour targeting a RASS of -2. A maximum infusion rate of 1.4 µg/kg/h are allowed.

Placebo group

The placebo group are treated as the intervention group, besides receiving glucose 5% infusion without Dexmedetomidine.

Polysomnography

Eight EEG electrodes are placed on the patients scalp at the left and right frontal lobe, left and right central lobe and left and right occipital lobe, according to the international 10/20 system of electrode placement. Positioning is relative to the two electrodes placed on the mastoid region and the ground and reference electrode placed at the top center of the scalp. To differentiate REM sleep from NREM sleep and wakefulness, two extraocular (EOG) electrodes are placed to monitor eye movement. Two submaxillary and one chin electromyogram (EMG) electrodes are placed to monitor muscle tone. Further two EMG electrodes are placed on the proximal lateral crus to monitor leg movement. Heartrate and oxygen saturation are recorded using two-point ECG and finger plethysmography applied on the right index finger. All data are stored by the portable screener on a SD flash card to be transferred in order to be analyzed. Mounting the PSG are done according to the AASM guidelines[30].

The PSG is done using hardware and utensils from Somnomedics including Domino software (Somnomedics GmbH Am Sonnenstuhl 63 D-97236 Randersacker Deutschland). Calibration to ensure acceptable electrode impedance (<10 KΩ, otherwise electrodes are replaced) is conducted. Biocalibration will be done prior to each PSG recording to identify pattern of eyes-open and eyes-closed, wakefulness, as well as the appearance of eye movements. Scoring of the PSG will be done according to the American Academy of Sleep Medicine guidelines (AASM).

Study Objective and endpoints

Primary objective

To investigate the effect of dexmedetomidine on deep sleep/sleep quality compared to placebo.

Primary endpoint

Improvement of deep sleep/sleep quality of clinical significance determined by total sleep time and sleep efficiency.

Secondary objectives

To investigate dexmedetomidine compared with placebo's effect on a) sleep phases, b) daytime function and delirium.

Secondary endpoints

Sleep phases determined by PSG and daytime function and delirium determined by CAM ICU. Alertness and wakefulness determined by RASS

Randomization method

Randomization will be performed electronically in REDCap (browser based online case report form) with an allocation ratio of 2:1 for Dexmedetomidine and placebo respectively in blocks of 10 patients. The randomization numbers with corresponding allocation are stored with the REDCap data manager. The randomization codes corresponding with treatment regimen are sealed in nontransparent envelopes for the pharmacist to prepare either Dexmedetomidine or placebo. The envelope is stored with the hospital pharmacy. After preparing the medication labeling with randomization code and identification of the patient, the medication will be stored in the refrigerator for the attending nurse to collect and administer.

Blinding

The treatment code is not accessible for anyone employed in the ICU, thus only the data manager, the GCP-monitor and the pharmacy personnel preparing the study drug have access to the code. Sleep assessment will be evaluated randomly by an independent doctor having only the randomization code for identification, thus blinded to the order of the recordings. A second person checks for accuracy of the blinding. The code is not broken before all data are analyzed. The data manager, who has access to the randomization code, can be contacted in case of emergency unblinding.

Trial personnel

The trial personnel are doctors and nurses in the ICU at the hospital of Southwest Jutland. The personnel are trained in non-sedation and the use of Dexmedetomidine, both in theory and by supervised practice. The hospital pharmacy personal has been trained in preparing the study and placebo drug.

Recording and reporting of SAE (Serious adverse Event)

Only SAE's that are related to the study intervention will be recorded. These events are expected to be accidental extubation and discontinuations of central venous accesses, which require reinsertion within a few hours. Severe arterial hyper/hypotension, cardiac arrythmia or high fever related to infusion of the study drug will be recorded

Investigators will report SAE's according to the national standard operational procedures. Primary investigator and the study nurses will screen for AE's (Adverse Events), which is mandatory. SAEs will be registered in the electronic case record form (REDCap) and reported to the Data Monitoring and Safety Committee (DSMC) and the Ethics Committee. The attending physician decides if an AE is serious.

Approvals, ethics, dissemination, and data collection

The study was approved by the Danish National Committee on Health Research Ethics (ID:S-20180214). Registration in EudraCT (2017-001612-11DK) has been done and the trial is approved by the Danish Medicines Agency, hence monitored by the Good Clinical Practice (GCP) unit. Registration with the Danish Data Protection Agency has been done and all data collected are registered in the browser based online database REDCap, which applies with the GCP guidelines. Publication in peer reviewed journal has been planned.

Sample size

Sample size evaluation were based on similar work done by Alexopoulou and Eumorfia[28], reporting significantly improved sleep efficiency (100%*TST/total PSG time) in critically ill patients when treated with dexmedetomidine. They also reported sleep architecture for stages in their crossover study. Estimates for placebo response and variation in SWS percentage of total sleep time were

based on their work. Placebo is assumed to result in 0% of SWS sleep with common standard deviation of 7%. Using parallel design and assuming 10% difference in SWS time, a sample size of 12 subjects per treatment arm provide 80% power to detect statistically significant difference at 5% level using Wilcoxon-Mann-Whitney test. Using 2:1 random allocation ratio reduces power and approximately 12% more subjects are required. Randomizing a total of 30 subjects allows approximately 10% drop out rate.

Data:

Baseline equalization of the groups will be tested statically, and sleep efficiency/quality will be estimated in the two groups and compared using Wilcoxon-Mann-Whitney or T test according to distribution of the data. Adjustment for baseline characteristics will be performed if significant link has been proven using regression analysis. Data will be handled according to the intension to treat analysis principles. All data will be stored in the REDCap database which complies with international Confidentiality standards. Only the investigators and the data manager will have access to the data.

Two reports will be generated regarding the sleep data one using data the time frame 22 to 8.00 and one using data from 18 to 6.00.

Discussion

The trial investigates the potential benefit of Dexmedetomidine on clinically relevant endpoints. If a beneficial effect is shown, this would have a large impact on future treatment of mechanically ventilated critically ill patients. Primary investigator will by e-mail communicate the result of the study to the participants.

In the ICU one aims to restore normal circadian rhythm for non-sedated, non-delirious patients, hence mobilized and encouraged to stay awake during the day (8-22:00). At night Pharmacologic and non-pharmacologic measures are done for the patient to be sleeping. If the patient on the other hand present delirious symptoms, sleep induction might be necessary, even if it does not compile with a normal circadian rhythm to break a vicious circle. Hence the study report will contain sleep patterns for both sedation strategies (22 to 8.00 and 18 to 6.00).

Recording during two consecutive days has been planned as opposed to two days apart. Thus, the patient will exhibit the same degree of critical illness and encephalopathic state.

Trial status

Inclusion has started: May 23, 2018. Completion and final analysis are expected in summer 2021. Orion Pharma have no influence on the conduct of the study and the presentation of results. Paper and PhD thesis are expected to be written and completed in 2022 and published in a peer reviewed journal.

Competing interests:

The project receives financial and supervision support from Orion Pharma. The company is otherwise without influence on the design, interpretation of data and decision to publish the result. Mikael Sörberg is employed by Orion Pharma which has supported the project financially. The rest of the authors declare no competing of interest.

Funding Statement

A grant of 70.000 Euro and the study drug was provided by Orion Corporation. The financial support was provided in part to cover the expenses of the study and the researchers have no economic interests in the company.

Author contribution

PJJ and PT developed the theory. PJJ, PT, TK, MS and JO performed computations and developed the study design. JO wrote the manuscript and all authors discussed and contributed to the final version. Financial resources were contributed by TK.

Acknowledgement:

Toni Sarapohja, Senior Principal Biostatistician, Orion Corporation is acknowledged for statistical support.

Legends

Figure 1: Consort

Figure 2: Interventions during the 2-day study period

Abbreviations and definition of terms

SAE Serious Adverse Event

AASM American Asociation of Sleep Medicine

APACHE Acute Physiology and Chronic Health Evaluation

CAM-ICU Confusion Assessment Method for the ICU

CRF Case Report Form

ECG Electrocardiogram

GCP Good Clinical Practice

HR Heart Rate

ICU Intensive Care Unite

LOS Length of Stay

MV Mechanical Ventilation

NREM Non-Rapid Eye Movement sleep

PSG PolySomnoGraphy

RASS Richmonde Agitation Sedation scale

REM Rapid Eye Movement sleep

RR Respiratory Rate

SAE Serious Adverse Event

SAPS Simplified AcutePhysiologic Score

SOFA Sepsis-related organ failure assessment score

SUSAR Suspected Unexpected Serious Adverse Reaction

VT Tidal Volume

SAE Serious Adverse Event

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Figure 1

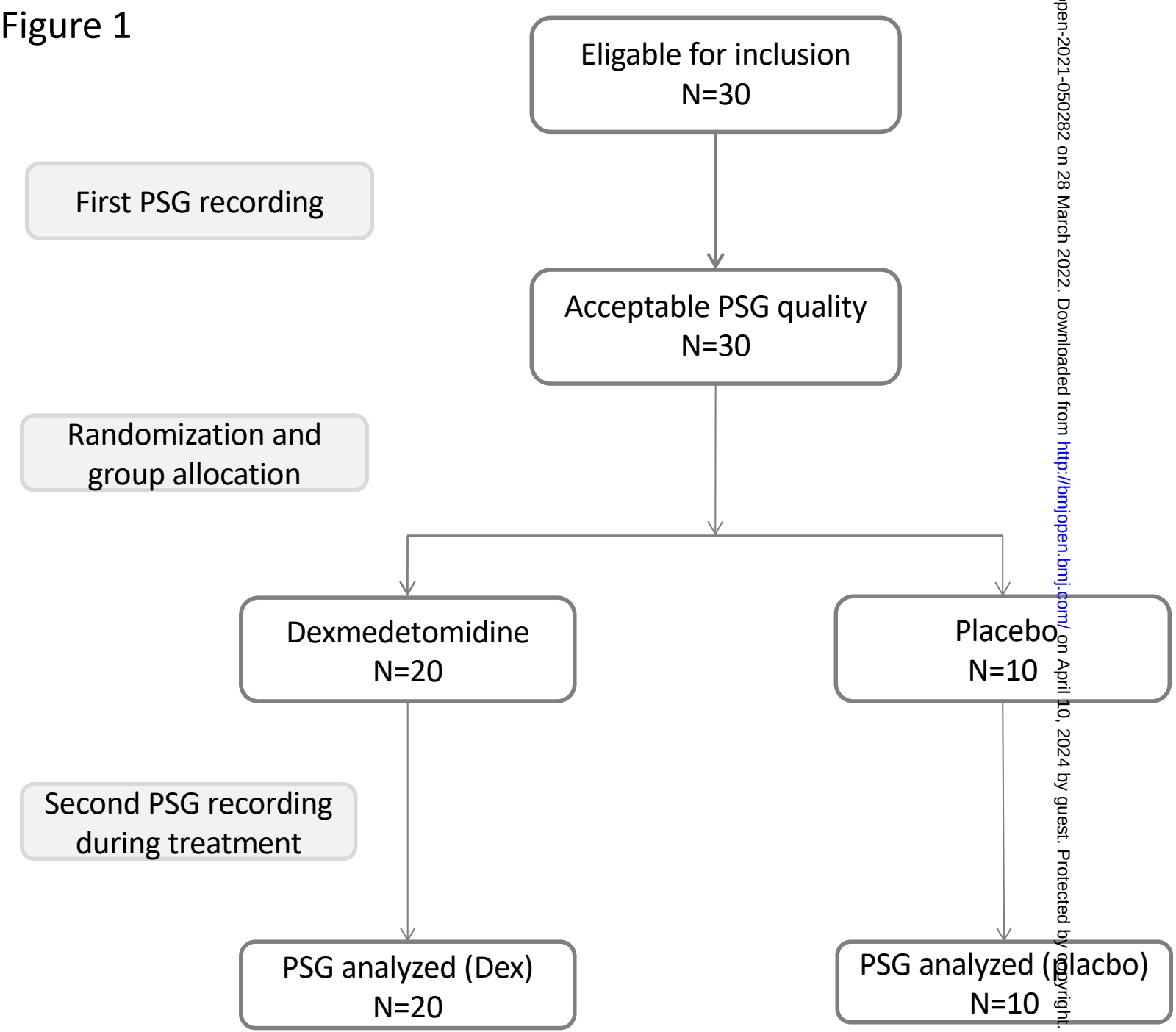
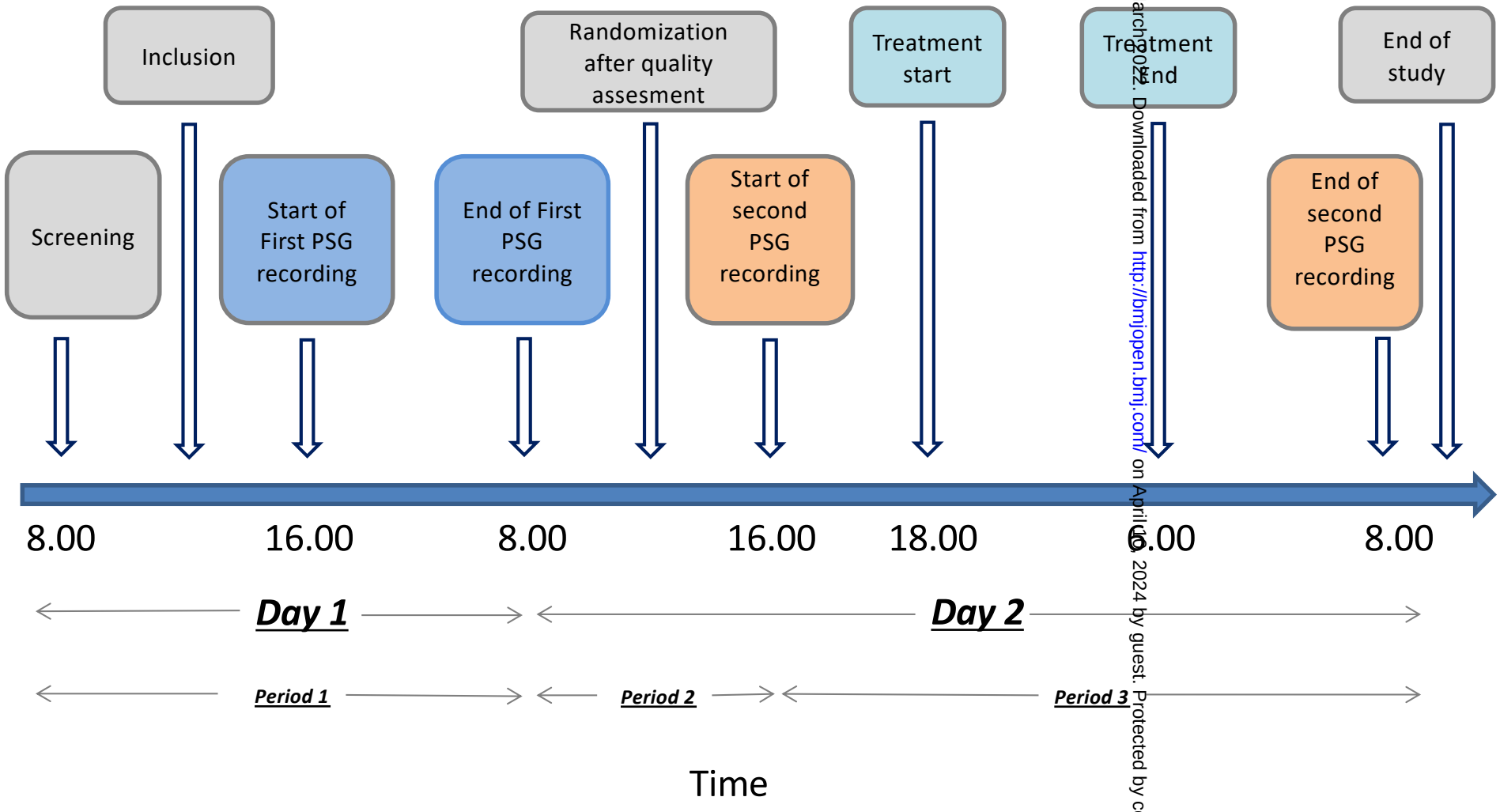


Figure 2



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
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	P9
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	P9
Protocol version	#3	Date and version identifier	P1-13
Funding	#4	Sources and types of financial, material, and other support	P10
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	P1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	P1
Roles and responsibilities: sponsor and funder	#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	P10
Roles and responsibilities: committees	#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)	P9
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	P3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	P3-4
Objectives	#7	Specific objectives or hypotheses	P4
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, non-inferiority, exploratory)	P3
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	P5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	P5

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P5
Interventions: modifications	#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)	P9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	P9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P6
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	P7
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)	P6
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	P9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	P5
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	P8

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	P8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P8
Methods: Data collection, management, and analysis			
Data collection plan	#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	P5-6
Data collection plan: retention	#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	P6-7,10
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	P6-7,10
Statistics: outcomes	#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	P10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P10

Statistics: analysis population and missing data	#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)	P10
Methods: Monitoring			
Data monitoring: formal committee	#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	P9
Data monitoring: interim analysis	#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	P9
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	P9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	P9
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)	P9
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P5,9
Consent or assent: ancillary studies	#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	P9-10

		participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	P10
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P10
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	
Dissemination policy: trial results	#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	P10
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	P11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	P9
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