The impact of nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit (UNDERPIN-ICU): A study protocol

for a multi-centre, stepped wedge randomized controlled trial

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Abstract

*Background:* Delirium is a common disorder in Intensive Care Unit (ICU) patients and is associated with serious short- and long-term consequences, including re-intubations, ICU readmissions, prolonged ICU and hospital stay, persistent cognitive problems, and higher mortality rates. Considering the high incidence of delirium and its consequences, prevention of delirium is imperative. This study focuses on a program of standardized nursing and physical therapy interventions to prevent delirium in the ICU, called UNDERPIN-ICU (nUrsiNg DEliRium Preventive INterventions in the ICU).

*Objective:*To determine the effect of the UNDERPIN-ICU program on the number of delirium-coma-free days in 28 days and several secondary outcomes, such as delirium incidence, the number of days of survival in 28 and 90 days and delirium-related outcomes.

*Design and Setting:* A multicenter stepped wedge cluster randomized controlled trial.

*Methods:* Eight to ten Dutch ICUs will implement the UNDERPIN-ICU program in a randomized order. Every two months the UNDERPIN-ICU program will be implemented in an additional ICU following a two months period of staff training. UNDERPIN-ICU consists of standardized protocols focusing on several modifiable risk factors for delirium, including cognitive impairment, sleep deprivation, immobility and visual and hearing impairment.

*Participants:*ICU patients aged ≥ 18 years (surgical, medical, or trauma) and at high risk for delirium, E-PRE-DELIRIC ≥35%, will be included, unless delirium was detected prior ICU admission, expected length of ICU stay is less then one day or when delirium assessment is not possible.

*Discussion:* For every intervention the balance between putative benefit and potential unwanted side effects needs to be considered. In non-ICU patients, it has been shown that a similar program resulted in a significant reduction of delirium incidence and duration. Recent small studies using multi component interventions to prevent delirium in ICU patients have also shown beneficial effect, without unwanted side effects. We therefore feel that the proportionality of potential positive effects of the UNDERPIN-ICU program, weighed against potential unwanted side effects is favourable. Since this has not been rigorously proven in ICU patients, we will study the effects of this program in ICU patients using a stepped wedge design.

*Trial registration:* Intended registry: <https://clinicaltrials.gov/>. This will be done when the final version of this manuscript is accepted.

*Reporting method:* Standard Protocol Items: Recommendations for Interventional Trails (SPIRIT).

*Keywords:* Adult; Critical care; Delirium; Intensive care; Intervention study; Nurses; Randomized Controlled Trial

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**What is already known about the topic?**

* Delirium is a common syndrome in ICU patients and associated with poor outcomes, therefore preventing ICU delirium is imperative.
* In non-ICU patients, it has been shown that the use of a multi component non-pharmacological intervention program resulted in a significant reduction of delirium incidence and duration.
* The use of non-pharmacological interventions, in which nurses play an important role, represents a promising strategy for delirium prevention in the ICU. Currently, there is insufficient evidence regarding the effects of a such interventions on delirium in the ICU.

**What this paper adds**

* A multicenter stepped wedge cluster randomized controlled trail will be conducted to determine the effect of using a multi component non-pharmacological intervention program on the number of delirium free days in the ICU.
* ICU outcome measures like ICU length of stay, number of days of survival and delirium incidence, as well as patient reported outcome measures, like quality of life and cognitive functioning, will be obtained.
* The intervention program consists of interventions targeting the modifiable delirium risk factors cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.

**1.** [**Introduction**](http://www.trialsjournal.com/authors/instructions/studyprotocol#formatting-background)

Delirium is defined as an acute disturbance in level of awareness, attention and cognition, with a fluctuating course, caused by a direct physical condition, and occurs over a short period of time.([1](#_ENREF_1)) Delirium is a serious disorder in critically ill patients in the Intensive Care Unit (ICU). The overall incidence of delirium in ICU patients is approximately 30%,([2](#_ENREF_2), [3](#_ENREF_3)) and even higher in patients admitted to the ICU for two days or longer.([4](#_ENREF_4)) It has serious short- and long-term consequences for ICU patients. Delirium is associated with prolonged duration of mechanical ventilation, length of stay in the ICU, and length of stay in the hospital.([2](#_ENREF_2), [4](#_ENREF_4)) During their ICU stay patients who suffer from delirium are more likely to involuntarily remove tubes and catheters compared to non-delirious patients, and the incidence of re-intubations and ICU readmissions is significantly higher than those without delirium. In addition, delirium leads to long-term cognitive problems, is associated with higher mortality rates and can influence long-term quality of life.([4-8](#_ENREF_4)) Moreover, delirium leads to a higher workload for ICU nurses([9](#_ENREF_9)) and a higher financial burden due to increased costs for the ICU as well as the hospital.([10](#_ENREF_10))

 Considering the high incidence of delirium and these serious consequences, reducing burdening by delirium is imperative, comprising delirium prevention as well as reducing the duration of delirium. Important in effectively preventing delirium is the early identification of high-risk patients, as optimal use of preventive measures is warranted in these patients because of their vulnerability.([11](#_ENREF_11)) A validated prediction model (the Early PREdiction of DELIRium IC (E-PRE-DELIRIC) model) allows a reliable calculation of the chance that a patient will develop delirium and may facilitate early identification of high-risk patients.([12](#_ENREF_12)) With use of such a delirium prediction model it has been shown that prophylactic pharmacological treatment with haloperidol may have important beneficial effects in patients at high risk for delirium, including a significant decrease in delirium incidence and an increase in the number of delirium free days in 28 days.([13](#_ENREF_13)) Despite the beneficial effects of haloperidol, the incidence of delirium remained rather high in high risk patients. Therefore, there is need to investigate alternative (non-pharmacological) interventions aimed at preventing delirium and its deleterious consequences.

 Multiple risk factors are associated with delirium.([14](#_ENREF_14), [15](#_ENREF_15)) Hence, a multi component intervention targeting several risk factors represents a promising strategy for delirium prevention.([16](#_ENREF_16)) In non-ICU patients, it has been shown that a program with standardized interventions focusing on several modifiable delirium risk factors, including cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment, resulted in a significant reduction of the delirium incidence and duration.([17](#_ENREF_17), [18](#_ENREF_18)) These interventions do not seem to be associated with significant harm for the patients.([16](#_ENREF_16)) In ICU patients, data of such a program consisting of standardized interventions are lacking. However, in studies focusing on specific parts of the program beneficial effects have been reported.([19-22](#_ENREF_19)) Recent studies using a non-pharmacological multi component intervention program to prevent delirium in the ICU yielded insufficient proof regarding the efficacy of the program, as a consequence of the used study designs, the limited sample size and problems with data collection.([23-25](#_ENREF_23)) Therefore, further research using a more rigorous design and a larger sample size in multiple ICUs is needed, also including an estimation of the efficacy and cost-effectiveness of the program.

 During this current study we will implement a multi component program including non-pharmacological nursing and physical therapy interventions aimed at delirium prevention in the ICU. This program, called UNDERPIN-ICU program (nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit), consists of standardized multi component interventions tailored to ICU patients([26](#_ENREF_26), [27](#_ENREF_27)) and focuses on delirium risk factors that can be influenced by nursing and physical therapy interventions: cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.

*1.1 Objectives*

The primary objective of this study is to determine the effect of the UNDERPIN-ICU program on the number of delirium-coma-free days in 28 days.

*The secondary objectives are threefold:* to determine the effect of the UNDERPIN-ICU program on: delirium incidence; the number of days of survival in 28 and 90 days; delirium-related outcomes; ICU and hospital length of stay; Quality of Life (QoL) and cognitive function of ICU patients, to determine the effect of the UNDERPIN-ICU program in different subgroups: e.g. admission type, predicted delirium risk), and lastly to assess the cost-effectiveness of the UNDERPIN-ICU program.

**2. Methods**

*2.1 Reporting method*

Following the Standard Protocol Items: Recommendations for Interventional Trails (SPIRIT 2013) – checklist.([28](#_ENREF_28))

*2.2 Study design and setting*

This study will be conducted using a multicentre stepped wedge cluster randomized controlled trial.([29](#_ENREF_29), [30](#_ENREF_30)) Eight to ten Dutch ICUs from both academic and general hospitals are selected based on their membership of the Dutch ICU Delirium Consortium as well as their commitment to improve their quality of care regarding ICU delirium. At baseline all ICUs will simultaneously start with the control period. The order in which an ICU will move to the intervention period will be randomized. Every two months the UNDERPIN-ICU program will be implemented in an additional ICU. From that point on the UNDERPIN-ICU program will be part of the standard care in that ICU. In each ICU two months of staff training will be provided, after which the ICU moves from control to intervention (Figure 1). Every ICU will participate for the entire study period. We chose this design since implementation of the program is only feasible at ward level, because randomization at patient level would result in contamination between patients in the intervention group and patients in the control group.([31](#_ENREF_31)) This contamination could possibly result in a diluted effect of the program including risk for a false-negative outcome.



*Figure 1: Timeline and randomization (C: control, T: training, I: intervention)*

Importantly, based on current evidence ([17](#_ENREF_17), [24](#_ENREF_24)) we expect these interventions will do more good than harm, so therefore there is little likelihood for the need to ‘de-implement’ the intervention at the end of the study.

*2.3 Eligibility criteria for patients*

In order to be eligible to participate in this study, patients should be: aged ≥ 18 years; surgical, medical or trauma patients; admitted to one of the participating ICUs and at high risk for delirium (>35% determined with the E-PRE-DELIRIC prediction tool).([12](#_ENREF_12)) Patients will be not eligible if they: are delirious before ICU admission; have an ICU stay < one day; if reliable assessment for delirium is not possible due to: sustained coma during complete ICU stay defined as Richmond agitation sedation score (RASS)([32](#_ENREF_32)) of -3/-4/-5; serious auditory or visual disorders; inability to understand Dutch; severely mentally disabled; serious receptive aphasia.

*2.4 Interventions*

The UNDERPIN-ICU program consists of interventions tailored for ICU patients focusing on the modifiable delirium risk factors: visual and hearing impairment, to prevent or treat sensory deprivation and ultimately the loss of orientation; sleep deprivation,to minimize/avoid sleep deprivation; cognitive impairment to (re)orientate patients with regard to time, place and person to prevent or minimize decline; and immobility, to improve patients’ functional mobility in the ICU and to stimulate patients’ cognition (table 1). These interventions are based on scientific literature as well as a Delphi study and a pilot study.([26](#_ENREF_26), [27](#_ENREF_27)) See Appendix A for the complete UNDERPIN-ICU program.

*2.5 Outcomes*

The primary outcome of the study is the number of delirium-coma-free days in 28 days. Secondary outcomes are: delirium incidence; the number of days of survival in 28 and 90 days; delirium-related outcomes including: duration of mechanical ventilation, incidence of re-intubation, or restart of mechanical ventilation in case of tracheostomy patients, incidence of ICU re-admission, unplanned removal of tubes/catheters, and the use of physical restraints; ICU and hospital length of stay; QoL and cognitive function of ICU patients at ICU admission (baseline), and three and twelve months after ICU discharge; an exploratory subgroup analyses (e.g. based on admission type, predicted delirium risk); a process evaluation to explain the effects based on adherence to the interventions; and a cost-effectiveness analysis which will include an economic evaluation.

*2.6 Participant timeline*

Baseline characteristics of the patient (e.g. age, gender, predicted delirium risk score,

APACHE-II score) will be collected. In order to detect delirium all consecutive patients will be screened by well trained nurses using the validated Dutch translation of the CAM-ICU at least once each shift (more often if indicated, like during periods of fluctuating symptoms or levels of sedation).([33](#_ENREF_33), [34](#_ENREF_34)) This screening is part of the daily ICU care. Before the study starts, all ICU nurses will receive a refresher course concerning the CAM-ICU on top of their in-house CAM-ICU training. This to guarantee a similar level of expertise in every participating centre regarding delirium assessment. (See Figure 2.)

 All primary and secondary parameters collected during this study are already routinely registered in the participating ICUs. During the two-month training period of the UNDERPIN-ICU program, no data will be collected.



*Figure 2: Participant timeline*

*2.7 Sample size*

Sample size of the study is calculated to detect a clinically relevant effect on the number of delirium-coma-free days in 28 days (primary outcome). The UNDERPIN-ICU program is considered to be effective if the number of delirium-coma-free days increases from 20 to 22 days in the high-risk group at the end of the study, with a standard deviation of 5. This difference is considered to be clinically relevant. A standard stepped wedge design (i.e., one cluster switches at each step) of 10 clusters with 14 measurement periods having 12-13 patients/period/cluster provides more than 80% power to detect the above difference for an alpha=.05 and ICC=.01 for clustering at ward levels (10x14x12.5=1750 ICU patients).([35](#_ENREF_35)) Based on other cohort studies, recruitment of 6-7 high-risk patients/month/ICU (so 12-13 per measurement period of two months) is considered feasible.

*2.8 Recruitment*

All patients admitted to the ICU will be screened for their risk for delirium as part of standard care. Patients at high risk for delirium will be included in the study as soon as possible after ICU admission. Due to the relative early onset of delirium after ICU admission the UNDERPIN-ICU program needs to be started as quickly as possible to optimize the possibilities for the UNDERPIN-ICU program to be effective.

*2.9 Assignment of interventions*

The UNDERPIN-ICU program used in this study will become standard treatment in all participating ICUs. (See Figure 1.) These ICUs will be assigned to the intervention based on cluster randomisation. This means that the moment of implementation of the UNDERPIN-ICU program per ICU will be determined randomly in this study. During the study, every participating ICU will implement the program.

 Randomization will be performed at the start of the study. By nature of the interventions, this study cannot be blinded.

*2.10 Data collection and management*

The start of data collection for this study is planned for January 2017.

*2.10.1 Delirium diagnosis*

Patients will be diagnosed as delirious when they have at least one positive delirium screening (confusion assessment method (CAM)-ICU)([33](#_ENREF_33), [34](#_ENREF_34)) during their complete ICU stay or when they are treated for delirium with haloperidol (without a positive CAM-ICU screening). The duration of delirium is defined as time from the first positive CAM-ICU or treatment with haloperidol, until the beginning of two consecutive days of negative delirium screenings. For ICU patients this is defined as a negative CAM-ICU screening, and when on the ward a Delirium Observation Screening (DOS) scale < 3).([36](#_ENREF_36)) Reoccurrence of delirium, defined as a new delirium episode occurring after a minimum of 48 hours of negative delirium scores, will be documented.

*2.10.2 Delirium-coma-free days in 28 days*

This is defined as the number of days a patient is not delirious and not in coma in 28 days starting from the day of inclusion in the study. A delirium-coma-free day is defined as a non-delirious day with a RASS([32](#_ENREF_32)) greater than -3/-4 or -5.

*2.10.3 Survival days in 28 and 90 days*

This is defined as the number of days that patients survive in 28 and in 90 days.

*2.10.4 Duration of mechanical ventilation*

This is the registered time in hours that the patient is on the mechanical ventilator before successful extubation. When the patient is ventilated mechanically several times during one admission, the ventilator times will be added. Both invasive and non-invasive ventilation will be registered.

*2.10.5 Incidence of re-intubation*

Patients who need to be intubated within 28 days after ICU admission, following a previous extubation, irrespectively the reason for re-intubation, will be counted as incident case for re-intubation.

*2.10.6 Incidence of ICU re-admission*

Patients who need to be readmitted to the ICU within 28 days, irrespectively the reason for readmission, will be counted as incident cases for ICU readmission.

*2.10.7 Incidence of unplanned removal of tubes/catheters*

Incidents in which patients remove their tube or catheter themselves will be counted as incident cases for unplanned removal. The period in which this is measured is during patients’ ICU stay or during the period when the patient is delirious (in case a patient is discharged to the ward) with a maximum of 28 days.

*2.10.8 Incidence of physical restraints*

Patients who need physical restraints (fixation of their limbs to prevent them from removing tubes or lines) within 28 days, will be counted as incident cases for physical restraints.

*2.10.9 ICU- and hospital length of stay*

This is defined as the number of days a patient is admitted to the ICU. Hospital length of stay is defined as number of days a patient is admitted to the hospital.

*2.10.10 Quality of Life (QoL) and cognitive function of ICU patients*

QoL will be assessed using the Short Form (SF)-36® Health Survey questionnaire. This is a validated quality of life questionnaire existing of physical and mental components distributed over eight items.([37](#_ENREF_37), [38](#_ENREF_38)) In addition, cognition will be assessed using the validated self-reporting cognitive failure questionnaire (CFQ).([39](#_ENREF_39)) This validated self-evaluating questionnaire consists of 25 items([39](#_ENREF_39)) and four dimensions of cognition: memory, distractibility, blunders, and (memory for) names.([40](#_ENREF_40))

 Patients will be asked to complete the questionnaires at baseline/ICU admission, three months after admission and one year after admission. When the patient at admission is not able to complete the QoL questionnaires, patient’s next of kin will be asked to complete the questionnaires, as they can also reliable assess the quality of life on admission to the ICU.([41](#_ENREF_41))

*2.10.11 Exploratory analysis*

For exploratory analysis data will be collected about admission type (surgical, medical or trauma) and predicted delirium risk (determined with a delirium prediction model (E-PRE-DELIRIC) for ICU patients).

*2.10.12 Process evaluation and cost-effectiveness*

A process evaluation will be performed to determine the relation between both the compliance to the interventions and contextual factors of the different ICUs on the effects that will be measured within the UNDERPIN-ICU study. In addition, the quality of the delirium assessments will be measured. Process data on the execution of the different interventions will be collected by performing real time observations of the activities of the ICU nurses and patients to determine the adherence to the interventions. Also, questionnaires will be used to determine both the baseline standard of care per ICU during the control period and the adherence of the ICU nurses to the interventions during the intervention period. In addition, observations of contextual factors like ward characteristics of the different participating ICUs will be performed.

Since costs for patients scoring positive for delirium are higher compared to non-delirium patients,([10](#_ENREF_10)) an improvement in delirium outcome as a result of the UNDERPIN-ICU program may result in cost-effectiveness. The cost-effectiveness analysis will include an economic evaluation divided over two parts. First, on patient level volumes of care will be measured prospectively over the in-hospital time path of study. Second, per modality standard cost-prices will be determined using the Dutch guideline completed by real cost prices via activity based costing.([42](#_ENREF_42), [43](#_ENREF_43))

*2.11 Data management*

All data will be collected electronically in an Electronic Clinical Report Form (E-CRF). This is a secured website to which all participating ICUs need to log in with a unique password to add data of their subjects’ study parameters. Data handling will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens WBP). Participating ICUs only have access to their own data. The key to the login codes will be safeguarded by the investigator.

*2.12 Statistical analyses*

Descriptive statistics will be presented as mean ± SD or median and interquartile ranges, depending on distribution. Continuous outcomes (e.g., QoL, cognitive function) will be compared between groups using linear multilevel models (patients nested within ICUs). If necessary, continuous skewed data (e.g., number of delirium-free days, length of stay) will first be log-transformed. Binary outcomes (e.g., delirium) will be compared between groups using logistic multilevel models. For time to event outcomes (e.g., survival time within 28 days), a multilevel Cox proportional hazard model (frailty model with random effect for ICU) will be used.([44](#_ENREF_44)) Two problems with the data are foreseen to possibly occur. First, due to the limited number of clusters the multilevel models, especially the frailty model and the logistic multilevel model, may not converge. In that case, clusters (ICUs) will be fitted as fixed effects or a summary measures approach will be employed. Second, data may be too far from normally distributed, so that they are not sufficiently normalized by log transformation (and, due to the limited number of clusters, one cannot rely on the robustness of regression analysis against non-normality that occurs for large samples). In that case, non-parametric tests, dichotomization of data by sensible cut-offs, or permutation tests (based on the parametric tests) will be considered for inference.

 Data will be analysed according to the ‘intention to treat’ principle, but in secondary analyses we will also carry out per protocol analyses. Missing value analysis will be performed and if necessary, missing data will be imputed using multiple imputations. Statistical significance is defined as a P-Value < 0.05. Data will be analysed using IBM® SPSS® Statistics or SAS® software.

*2.12.1 Primary study parameter*

The main analysis is the comparison of delirium-free days without coma between the intervention and control groups.

*2.12.2 Secondary study parameters*

The data of the secondary study parameters will be presented quantitatively and compared between intervention and control groups.

*2.12.3 Exploratory analysis*

The influence of potential prognostic covariates, e.g., admission type and predicted delirium, risk will be investigated by including each of these as covariates and their interaction with the intervention in regression analyses. Additionally, the influence of these will be graphically investigated using subgroup analyses (forest plots).

*2.12.4 Analysis process evaluation and cost-effectiveness*

During the process evaluation analysis, the data from the effect - and process evaluation will be merged to get insight in the relation between the effectiveness of the UNDERPIN-ICU program and the process consisting of compliance to the interventions and contextual factors. To determine the quality of the delirium assessments, interrater reliability measurements of the CAM-ICU will be performed, followed by the calculation of the Cohen's kappa coefficient.

 Cost-effectiveness will be analysed by comparison of delirium-free days as well as by compliance to the interventions between the intervention and control group. Also cost-effectiveness ratio will be expressed as cost per delirium-free day gained and cost per Quality Adjusted Life Year (QALY) gained.([45](#_ENREF_45)) Furthermore, a budget impact analysis will be conducted to assess how health care budgets are changed when offering the UNDERPIN-ICU program.

*2.13 Monitoring*

During this study, data will be monitored. The participating ICUs will be monitored before as well as after implementation of the UNDERPIN-ICU program. A random patient sample will be checked regarding the eligibility for inclusion and source data verification of the primary outcome measure and several secondary outcome measures will be performed.

*2.13.1 Harms*

Adverse events (defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the intervention) reported spontaneously by the patient or observed by the investigator or staff will be recorded.

*2.13.2 Auditing*

Compliance to the UNDERPIN-ICU program will be measured by performing observations and the use of registration lists for both ICU nurses as well as participating observations and measurements using electronically supportive devices.

*2.14 Ethics*

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Handling of the data will comply with the Dutch Personal Data Protection Act. The study has been approved by the MREC region Arnhem-Nijmegen (No. NL2013/173). The need for informed consent was waived, because the UNDERPIN-ICU program is a change in health care policy to a package of evidence based interventions of which the effect is evaluated, for which no explicit consent of the patient is necessary. Nevertheless, all included patients will receive written information about the study.

*2.14.1 Access to data*

All investigators have access to their local trial data during the study period. After termination of the data collection period only the authors of the final manuscript, monitors and legal representatives will have access to the data, which will be stored in a Trusted Digital Repository. After termination of the study, the anonymised data will be made available for future research.

*2.14.2 Ancillary and post-trial care*

Since the participating ICUs will adjust their standard care to include the UNDERPIN-ICU program, no additional provisions are needed for the participants. Participants will not receive any compensation.

*2.14.3 Dissemination policy*

Regardless of the results of the study, the results will be shared via presentations on (inter-) national congresses and published in peer reviewed scientific journals, preferably trough open access. Authorship will comply with the recognized ethical standards concerning publications and authorship, established by the International Committee of Medical Journal Editors. Also, the results will be disseminated using social media and integrated in our existing DeliriumICU app which is word widely available. When the program will harm the patients, a de-implementation plan will be developed and executed in the participating centres.

**3. Discussion**

Prevention of delirium in the ICU is very important as delirium is a common disorder in ICU patients, resulting in negative consequences.([2](#_ENREF_2)) Non-pharmacological multicomponent interventions targeting several modifiable delirium risk factors represent a promising prevention strategy.([16](#_ENREF_16), [46](#_ENREF_46)) However, the effectiveness of a program consisting of such interventions is not yet rigorously studied in ICU patients.([23-25](#_ENREF_23)) In this study, we will implement the UNDERPIN-ICU (nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit) program and study its effect on delirium in ICU patients. With this study we aim to decrease the burden of delirium for ICU patients, as well as study the effect of the UNDERPIN-ICU program on cost-effectiveness in the ICU. If our UNDERPIN-ICU study indeed demonstrates positive effects of non-pharmacological interventions on ICU delirium and (cost)-effectiveness, it will change the care for ICU patients on a large scale.

 This current study has several strong features. The design, a stepped wedge cluster randomized controlled trial, can provide strong evidence of the effectiveness of the UNDERPIN-ICU program and indicates higher quality than results from non-randomized trials.([47](#_ENREF_47)) In addition, this design is beneficial due to an increased statistical power as a result of both between and within group comparisons.([48](#_ENREF_48)) Also, the design facilitates phased implementation resulting in a decreased risk for contamination between study groups([49](#_ENREF_49)) and less risk of bias since all ICUs can be trained in performing the UNDERPIN-ICU program by the same persons (PR, MvdB). The UNDERPIN-ICU program has a strong foundation as it is based on literature as well as expert and patient opinion. The use of a literature review provided a scientific base for the draft intervention program, and during both a Delphi study and a pilot study the UNDERPIN-ICU program was tailored to ICU patients.([26](#_ENREF_26), [27](#_ENREF_27)) In addition, currently the implementation of an intervention program is recommended for ICU delirium management including prevention strategies.([50](#_ENREF_50)) The use of an intervention program already has been shown effective in improving other ICU outcomes like acute kidney injury and sepsis.([51](#_ENREF_51), [52](#_ENREF_52))

 Nowadays an important aspect regarding a newly developed intervention program like the UNDERPIN-ICU program, is its cost-effectiveness.([53](#_ENREF_53)) As delirium is associated with an increased length of stay,([2](#_ENREF_2)) and a delay in transfer to a general ward is costly,([54](#_ENREF_54)) improving ICU efficiency and optimizing cost-effectiveness by delirium prevention is essential. Therefore, the cost-effectiveness of the UNDERPIN-ICU program will be part of the analysis of this study.

 There are also some limitations that need to be addressed. As we will implement the UNDERPIN-ICU program as a whole per cluster, the contribution per individual intervention will not be clear from the primary study results. Therefore we will perform a process analysis to assess which intervention or contextual factor inhibited of promoted the effectiveness of the UNDERPIN-ICU program.([55](#_ENREF_55)) It should be taken into account that despite the fact that this study will be conducted in multiple Dutch ICUs from both academic and general hospitals, our results may not be globally generalisable because of possible differences in ICU logistics and resources as well as in cultural aspects.([56](#_ENREF_56)) Although local tailoring consisting of minor modifications of the UNDERPIN-ICU program may be needed, we believe that the main conclusions of our study will be generally valid.

**Declaration of interests**

The authors declare they have no competing interests.

**Anonymity**

In view of the double blind review process the authors chose not to include author names in the paragraph ethics, the acknowledgements, funding and in reference number 26 and 27.

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**What is already known about the topic?**

* Delirium is a common syndrome in ICU patients and associated with poor outcomes, therefore preventing ICU delirium is imperative.
* In non-ICU patients, it has been shown that the use of a multicomponent non-pharmacological intervention program resulted in a significant reduction of delirium incidence and duration.
* The use of non-pharmacological interventions, in which nurses play an important role, represents a promising strategy for delirium prevention in the ICU. Currently, there is insufficient evidence regarding the effects of a such interventions on ICU delirium.

**What this paper adds**

* A multicenter stepped wedge cluster randomized controlled trail will be conducted to determine the effect of using a multicomponent non-pharmacological intervention program on the number of delirium free days in the ICU.
* ICU outcome measures like ICU length of stay, number of days of survival and delirium incidence, as well as patient reported outcome measures, like quality of life and cognitive functioning, will be obtained.
* The intervention program consists of interventions targeting the modifiable delirium risk factors cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.

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| --- |
| **Table 1. Highlights of the UNDERPIN-ICU program** |
| *1.Visual and hearing impairment* | Use of visual and hearing aids whenever awake.Approach from the best visual and hearing side.Provision of material adapted to visually impaired patients.Prevention of cornea dehydration during sedation.Attention to verbal communication when severely visually impaired.Limiting background noise.Use of special communication techniques as appropriate |
| *2. Sleep deprivation* | Optimizing circadian rhythmNoise reductionMinimizing night-time procedures.Providing optimal relaxationRestriction of sleep medicationImproving staff awareness of sleep importanceStrive to minimize sedation use. |
| *3 Cognitive impairment* | Placing a schedule, clock and calendar for each patientPromote provision of personal objects by next of kinPromote regular visitsOptimizing and tailoring communication based on patients preferencesFrequent reorientation Provision of cognitive training exercises. |
| *4. Immobility* | Encouraging setting and documenting of clear mobilisation goalsMinimalizing sedation useMinimizing and optimally locating restraining lines Optimizing analgesia and proper guidance for minimalizing pain and fear during mobilization.Frequent provision of physical therapy and/or mobilization, tailored to physical stateInvolve next of kin in stimulating early mobilisation |
| *A full description of activities for each theme can be found in appendix A.* |

**Appendix A The UNDERPIN-ICU program**

*1. Visual and hearing impairment*

*Aim:* to prevent or treat sensory deprivation and ultimately the loss of orientation.

Ensure there is a clear note in the patients’ file in case of visual and/or hearing impairment and what types of visual or hearing aids the patient is using.

*Notes added to the intervention: whenever an electronic patient data management system*

*is available a reminder should be built in to make sure visual and hearing impairment is*

*discussed during the admission interview and that the patient’s family is asked to bring*

*any visual or hearing aids including an instruction how to use them to the ICU.*

Visual protocol:

1. Ensure that the patients use their visual aids whenever they are awake.

*Notes added to the intervention: e.g. use glasses or magnifier, in case a patients wants to use contact lenses the patient should be able to insert and remove the lenses by themselves. Pay attention to pressure ulcers due to devices during repositioning.*([57-62](#_ENREF_57))

1. Ensure that visual aids are clean before use.
2. Approach the patient from the side at which he or she has good vision.
3. Provide material adapted to visually impaired patients, like large-print books, electronic books (iPad) or fluorescent tape on call bell.([57-62](#_ENREF_57))
4. Prevent dehydration of the cornea during sedation.
5. Pay extra attention to verbal communication regarding the execution of (nursing) activities and describing the bedside, in case a patient is severely visually impaired.

Hearing protocol:

1. Ask the patient’s family to bring the patient’s hearing aids, including enough batteries and an instruction how to use them, to the ICU.
2. Ensure that the hearing aids are fully functional before use.
3. Ensure that the patients use their hearing aids whenever they are awake, remove the hearing aids in consultation with the patient during the night or moments of rest.

*Notes added to the intervention: pay attention to pressure spots due to the hearing aids during repositioning.*([57-62](#_ENREF_57))

1. Speak clear and limit background noise.
2. Approach the patient from the side at which he or she has good hearing.
3. Use special communication techniques, like easy (hand)gestures, writing, pictures/symbols, letter cards or new communication devices like an iPad.([57-62](#_ENREF_57))

*2. Sleep deprivation*

*Aim:* to minimize/avoid sleep deprivation.

1. Unit-wide noise-reduction strategies ([22](#_ENREF_22), [57](#_ENREF_57), [58](#_ENREF_58), [60-67](#_ENREF_60)):
	1. Quiet hallways, closed doors, no loud talking, provide colleagues with noise feedback. Vibrating beepers or telephones. Use of headphone when a patient listens to music or is watching television. Decrease alarm volume, expansion of alarm boundaries of the mechanical ventilator or monitor within safe levels.

*Notes added to the intervention: close doors of the patient’s room or other rooms like the staff room or utility room depending on the building and possibilities of the ICU.*

* 1. Avoid nursing and medical procedures during sleep time, taking into account the patient’s medical condition.

*Notes added to the intervention: use a schedule to make adjustments to allow sleep. These adjustments include a rescheduling of medication rounds (adjustment of the default time for medication gifts), blood draws, scheduling of vital signs measurement (minimize use of non invasive blood pressure measurements) and bundling of necessary nursing activities.*

1. Reduce ICU lights to a minimum during sleep time, unless necessary.([22](#_ENREF_22), [58](#_ENREF_58), [64-67](#_ENREF_64))

*Notes added to the intervention: automatically dim (turn off) the lights in (communal) rooms after a certain time. Use of a flashlight by nurses during the nightshift. Dimming of monitor screens and turning the machines out of the patient’s sight. Fend light by the use of curtains, luxaflex or lamellae.*

1. After consultation with the patient, apply earplugs (unless contra indicated), from start of the night shift until the end of the night shift.([66](#_ENREF_66), [68](#_ENREF_68))
2. Provide relaxation music when it is time to sleep, pay attention to noise disturbance.([57](#_ENREF_57), [66](#_ENREF_66))

*Notes added to the intervention: ask the patient’s family for help and advice regarding the patient’s music preference and if necessary to bring any devices.*

1. Ask the patient/family what the patient does at home to promote sleep and whenever permissible provide this to the patient.([67](#_ENREF_67))

*Notes added to the intervention: for example, read to the patient (by nurse, family or audio book), or when the patient has particular sleep objects, such as a certain pillow provide these. Keep hygiene rules in mind. You can ask this question during the admission interview.*

1. Be restrictive with the use of sleep medication, use a ward protocol in case you use sleep mediation.

*Notes added to the intervention: the ward protocol provides information regarding the choice of sleep medication, for example do not use sedation like midazolam or propofol, and the time of administration.*

1. Highlight the importance of good sleep in your ward by the use of flyers that ask attention for the reduction of light and noise during the night.
2. Provide a clear day structure by compiling a personal day program for the patient.
3. Discourage daytime sleep, by improving the sleep-wake cycle using bright light during the day.([21](#_ENREF_21), [60](#_ENREF_60), [63](#_ENREF_63), [66](#_ENREF_66), [69](#_ENREF_69))

*Notes added to the intervention: whenever necessary a short rest moment can be planned in a personal day program.*

1. Whenever fitting the patient’s individual treatment plan: strive to use sedation as less as possible. In case of sedation, perform a daily wake-up (reduce or stop sedation once a day) and pursue a RASS score of > -3 en < +2. Pursue a RASS of 0 in patients without sedation.([64](#_ENREF_64), [65](#_ENREF_65))

*Notes added to the intervention: in case the patient is having a RASS score outside the target levels: evaluate the cause and if possible take care of it. Use the ward protocol for this.*

1. Encourage (early) mobilization.([66](#_ENREF_66))

*3 Cognitive impairment*

*Aim:* to (re)orientate patients with regard to time, place and person to prevent or minimize decline.

Orientation protocol:

1. Place a board with the name of the patient’s nurse, intensivist and a day schedule in the patient’s sight.([57](#_ENREF_57))

*Notes added to the intervention: the day schedule is compiled using key words and symbols for activities like mobilization, sleeping, visiting hours.*

1. Provision of a clock and calendar in the patient’s room in the patients sight.([22](#_ENREF_22), [57](#_ENREF_57), [59](#_ENREF_59), [61](#_ENREF_61), [62](#_ENREF_62), [70](#_ENREF_70))

*Notes added to the intervention: it is important to keep track on whether the clock is working and the time and date are correct.*

1. In consultation with the patient’s family, take care of the presence of familiar objects in the patient’s room like own pillows, pictures or family photographs.([59](#_ENREF_59), [63](#_ENREF_63), [70](#_ENREF_70)) Let the patient watch television, listen to preferred music or read the paper or a magazine.([22](#_ENREF_22), [71](#_ENREF_71), [72](#_ENREF_72))

*Notes added to the intervention: if necessary let the family bring visual or auditory media from home (labelled with a name). It is important to follow the hygiene rules and have availability of WIFI.*

1. Facilitate regular visits from family and friends. Give the family a letter to explain preventive measures like reorientation and the presence of family or friends.([59](#_ENREF_59), [62](#_ENREF_62))

*Notes added to the intervention: provide wide visiting hours. Important is to inform the family about the care, treatment and rest moments of the patient and when the specific consultation meetings with healthcare staff are planned. Make clear arrangements about who may visit the patient and how many and how long visitors are allowed. Translate the letter into different languages.*

1. Discuss with patient’s next of kin how to call the patient (use of the first or last name).([22](#_ENREF_22))

*Notes added to the intervention: this subject might be part of the admission interview and should be documented in the patient’s file and on the board in his room (see intervention A).*

1. To get to know the patient his/her family and nurse compile a poster containing information about the patient’s preferred calling name, which devices the patient is using to support vision/hearing, what the patient does at home to promote sleep, favourite music, television programs, books, and hobbies, and other things important to the patient.
2. Orient the patient’s bed so they can perceive daylight/darkness ([63](#_ENREF_63)) and provide appropriate lighting fitting the time of the day.([61](#_ENREF_61)) Place patients with a long ICU length of stay in the rooms with most daylight.

*Notes added to the intervention: during the day time bright light, in the course of the evening dim the light and during the night as dark as possible. Decisive in the possibilities to be able to execute this intervention is the construction of the ICU.*

1. Ensure appropriate use of glasses (contact lenses) and hearing aids.([70](#_ENREF_70))
2. Ensure daily during the day shift that the patient is provided with simple and short information about the ward, hospital (i.e., hospital name, ICU length of stay), reason for hospitalization, and their illness progression (e.g. concerning diagnostic and therapeutic measures).([22](#_ENREF_22), [57](#_ENREF_57), [63](#_ENREF_63))

*Notes added to the intervention: it is important to provide uniform information (registered in the patient’s file). The nurse should also ask the patient what he or she already knows. Based on their own discretion nurses can repeat the information.*

At least every shift:

1. Stimulate the patient’s orientation as part of the daily routine by asking or explaining them what day is it and where they are.([22](#_ENREF_22), [57](#_ENREF_57), [63](#_ENREF_63))
2. Caregivers explain to the patient who they are, and what their role is, answer the patient’s questions and discuss the patient’s concerns whenever necessary.([58](#_ENREF_58), [61](#_ENREF_61), [62](#_ENREF_62))

Preliminary cognition training protocol:

*Aim:* to minimize/avoid cognitive decline*.*

Cognitive training for ICU patients consists of eleven trainings in total. Each day the ICU nurse will execute two of these cognitive trainings with the ICU patient. These trainings will be further elaborated in our article about the pilot study in which we determined the feasibility of cognitive training in ICU patients.([26](#_ENREF_26))

* Digit span: to train attention and short term memory
* Digit game: to train selective attention and (verbal) working memory
* Memory task: to train attention, working memory and long term memory
* Symbol searching: to train speed of information processing using visual perception and selective attention
* Digit cancellation task: to train selective attention and visual perception
* Blocks task: to train selective attention and (visual) working memory
* First and second names: to train speed of daily life memory
* Executive functioning: to train working memory and attention
* Bells test: to train selective attention
* Picture guess: to train reasoning and working memory
* Difference searching: to train selective attention and working memory

*4. Immobility*

*Aim:* to improve patients’ functional mobility in the ICU and to stimulate patients’ cognition.

1. With the exception of contra indications: optimize ICU patients’ sedation (pursue RASS 0) to permit (active) physical therapy, while retaining their comfort.([73](#_ENREF_73))

*Notes added to the intervention: for this stimulation of the day- and night rhythm is important.*

1. Reduce pain and fear as a hampering factor for mobilization, by taking care of adequate analgesia and proper guidance of the patient.
2. Physical therapy or mobilization supported by nurses should be performed at least once daily.([62](#_ENREF_62), [70](#_ENREF_70), [73](#_ENREF_73), [74](#_ENREF_74)).

*Notes added to the intervention: whenever possible more often.*

1. With the exception of contra indications: patients who are unresponsive due to coma (RASS -3/-4/-5), who are at risk for contractures, will receive passive motion exercises for all their limbs.([74](#_ENREF_74)) In addition, their position in bed should be changed every three to four hours to prevent the occurrence of pressure ulcers.([62](#_ENREF_62)) When patients are able to interact (RASS > -3 and < +2), physical therapy can consist of active (independent) exercises while the patient is lying on his back. When the patient tolerates these exercises the therapy can be extended to bed mobility activities, including upright sitting, sitting balance activities and exercising on a cycle movement device. These activities can be followed by participation in activities of daily living and exercises that encourage increased independence with functional tasks (e.g. sit-to-stand transfers from bed to chair), and finally pre-gait exercises and walking (if necessary with mechanical ventilation). Progression of activities should depend on patient tolerance and stability.([74](#_ENREF_74), [75](#_ENREF_75))
2. Whenever feasible, nurses and instructed family should initiate, encourage and remind patients to mobilize early or do motion exercises multiple times a day.([57](#_ENREF_57), [60](#_ENREF_60), [61](#_ENREF_61), [63-65](#_ENREF_63)) In addition, nurses stimulate active involvement during daily care activities.

*Notes added to the intervention: the physical therapist plays a stimulating and informing role in this.*

1. To promote and facilitate mobilization: the location of central lines and tubes should allow mobilization (preferably not in the groin). Daily evaluation of the necessity of immobilizing equipment (e.g., central lines, tubes, bladder catheters, or physical restraints). This equipment should be removed whenever possible.([57](#_ENREF_57), [62](#_ENREF_62)) If necessary central lines, tubes or catheters are temporarily disconnected or blanked off. In consultation with the patient’s family fixation can be disconnected in their presence.

*Notes added to the intervention: presence of family is stimulated.*

1. Per patient clear goals targeting mobilization are set and registered in the patient’s medical record. In addition, multi disciplinary consultation takes place to take care of the right timing of physical therapy regarding sedation and the day program.

*Notes added to the intervention: it should be known what mobilization is allowed and/or if the patient needs any devices for security reasons like a collar, corset or plaster helmet. Whenever possible the patient is informed about this and receives the necessary instructions.*

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