Improved Guideline Adherence and Reduced Brain Dysfunction after a Multicenter Multifaceted Implementation of ICU Delirium Guidelines in 3,930 Patients

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ABSTRACT

Objective

Implementation of delirium guidelines at ICUs is suboptimal. The aim was to evaluate the impact of a tailored multifaceted implementation program of ICU delirium guidelines on processes of care and clinical outcomes and draw lessons regarding guideline implementation.

Design

A prospective multicenter, pre-post, intervention study.

Setting

ICUs in one university hospital and five community hospitals.

Patients

Consecutive medical and surgical critically ill patients were enrolled between April 1, 2012, and February 1, 2015.

Interventions

Multifaceted, three-phase (baseline, delirium screening and guideline) implementation program of delirium guidelines in adult ICUs.

Measurements and Main Results

The primary outcome was adherence changes to delirium guidelines recommendations, based on the Pain, Agitation and Delirium guidelines. Secondary outcomes were brain dysfunction (delirium or coma), length of ICU stay and hospital mortality. A total of 3,930 patients were included. Improvements after the implementation pertained to: delirium screening (from 35% to 96%, $P<0.001$), use of benzodiazepines for continuous sedation (from 36% to 17%, $P<0.001$), light sedation of ventilated patients (from 55% to 61%, $P<0.001$), physiotherapy (from 21% to 48%, $P<0.001$) and early mobilization (from 10% to 19%, $P<0.001$). Brain dysfunction improved: the mean delirium duration decreased from 5.6 to 3.3 days (-2.2 days; 95% CI, -3.2 to -1.3, $P<0.001$), and coma-days decreased from 14% to 9% (RR 0.5; 95% CI, 0.4-0.6, $P<0.001$). Other clinical outcome measures, such as length of mechanical ventilation, length of ICU stay and hospital mortality did not change.

Conclusions

This large pre-post implementation study of delirium-oriented measures based on the 2013 PAD-guidelines showed improved health professionals' adherence to delirium

guidelines, and reduced brain dysfunction. Our findings provide empirical support for the differential efficacy of the guideline bundle elements in a real-life setting and provide lessons for optimization of guideline implementation programs.

INTRODUCTION

Delirium is a common form of vital organ dysfunction in critically ill adults, associated with increased morbidity, mortality, and long-term cognitive deterioration [1-3]. Adequate delirium management is therefore an important component of intensive care – as substantiated in the Pain, Agitation, and Delirium (PAD) guidelines [4]. Successful implementation of guidelines into daily practice is challenging [5] although multifaceted implementation programs have the potential to facilitate success [6]. Implementation of the PAD guidelines has had beneficial effects on pain, brain dysfunction, durations of mechanical ventilation and ICU stay, early mobilization, long-term cognitive dysfunction, functional recovery and mortality in the critically ill [7-9]. Still, "real-life" prospective multicenter implementation studies focused on these delirium-oriented guidelines in hospitals with low use of the guidelines at baseline are needed to bring clinical evidence into practice on a wider scale, given the suboptimal implementation of these guidelines worldwide [10].

We therefore performed the prospective multicenter 'ICU DElirium in Clinical PracTice Implementation Evaluation' (iDECePTIvE) study [11], designed to evaluate the effectiveness of a multifaceted implementation program tailored to improving adherence to delirium guidelines, and to study patient-related benefits.

MATERIALS AND METHODS

Study design and participants

We conducted a prospective, multicenter, before-after implementation study in six ICUs in the Netherlands - one university and five community hospitals (three teaching and two non-teaching hospitals) [11]. The size of the units varied between 8 and 32 ICU beds. Consecutive ICU patients older than 18 years old or older were included. Exclusion criteria were: a primary neurological diagnosis; home mechanical ventilation for chronic respiratory insufficiency; and burn-injuries. The intervention, an implementation program focused at the implementation of the delirium-oriented recommendations derived from Dutch ICU Delirium Guidelines [12] and the PAD-guidelines of the Society of Critical Care Medicine [4] – was aimed at all ICU physicians and nurses. Results of this study were reported using the Standards for Quality Improvement Reporting Excellence guidelines [13]. The study protocol was reviewed by the Medical Ethical Committees of participating hospitals (MEC-2012-063). Patients' informed consent was not necessary according to Dutch legislation [14]. The study was registered at Clinicaltrials.Gov (Identifier: Nct01952899 2017).

Procedures, Outcomes and Data Collection

The study duration was 36 months and consisted of three measurement periods between April 2012 and February 2015 **(Figure 1).** The Implementation Model of Change of Grol and Wensing [15] was used to structure the guideline implementation. This model is a 7-steps approach, and starts with identifying the problem and defining the aim of change followed by identification of potential barriers and facilitators for implementation; development of an implementation plan based on these barriers and facilitators; and finally, execution, evaluation and sustaining of the implementation plan.

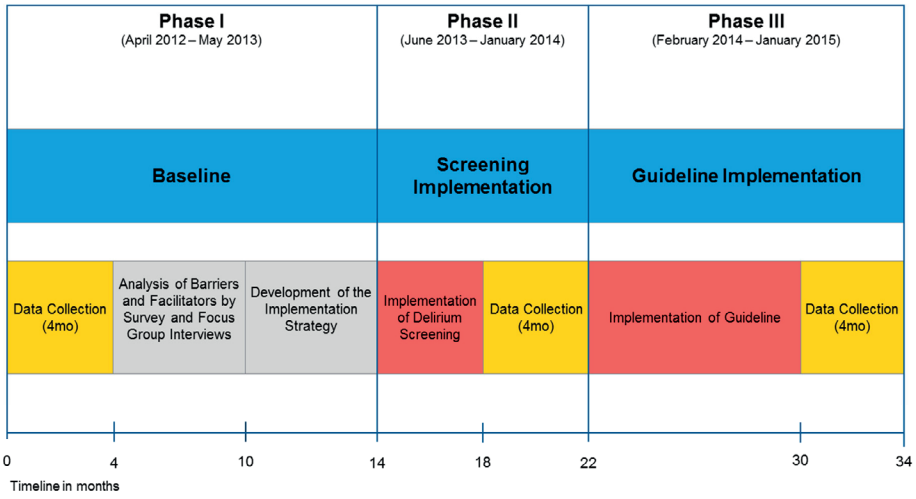

Figure 1: Timeline iDECePTIvE Study

Phase I

The baseline phase started with a 4-month data collection period. To avoid the Hawthorne effect [11], staff of the participating ICUs were not informed about the study during data collection, with the exception of the local intensivist (PI) and research nurses. Next, we performed an analysis of barriers and facilitators for delirium guideline adherence by means of a survey [16] and focus group interviews with stakeholders, and development of the implementation program **(Figure 1)**. We identified more than thirty barriers and facilitators for guideline adherence, to which we then tailored the implementation program following the model of Grol and Wensing and change theories [6,11,16,17]**(Appendix: supplemental digital content 1 and 2)**. Important facilitators were: realizing that delirium is a major problem, that treatment is essential, and that delirium is often under-diagnosed. The most important barriers were: insufficient knowledge for screening, no integral delirium protocol with a link to screening results [16]. The implementation program consisted of different implementation strategies in accordance to the Effective

Practice and Organization of Care group (EPOC) classification, mainly on organizational and professionals level [18,19]. See details in **Table 1** and **Figure 1.**

Phase II

This phase was dedicated to reliable delirium screening, for which all nurses and physicians compulsory completed an e-learning program. We formally appointed an intensivist and research nurse at each site to act as local champions during this and subsequent phases and encouraged them to involve other ICU nurses or ICU physicians as 'ambassadors'. Additional clinical lessons and bedside education were provided by the local implementation teams, which also performed delirium screening spot-checks. Three of the ICUs preferred the Confusion Assessment Method for the ICU (CAM-ICU) [20]; the other three preferred the Intensive Care Delirium Screening Checklist (ICDSC) [21]. All implementation elements are briefly explained in **Table 1** and were categorized according to the Cochrane Effective Practice and Organization of Care (EPOC) [18] and study phase.

Phase III

This phase consisted of 8-months of implementation followed by 4-months of data collection (**Figure 1**). The nurses and physicians now completed a second e-learning program focused on the guideline. Everyone received a laminated pocket-card summarizing the integrated measures based on the PAD-guidelines (Appendix: **Supplemental Digital Content 3a and b**).

Throughout the implementation phase, we regularly did bed-side reliability spot-checks on delirium screening, distributed delirium screening adherence feedback posters, issued newsletters on study progression and practical experiences, assessed the perceived level of implementation of bundle elements and the deployment of implementation elements as another feedback tool to the local implementation teams. Furthermore, experiences with the implementation program were shared in repeated focus group sessions.

Outcomes

The primary outcome was changes in adherence to guideline recommendations from before to after implementation. Secondary outcomes were: presence of brain dysfunction defined as days with delirium or coma, duration of mechanical ventilation, ICU length-of-stay (LOS), ICU and hospital mortality.

Data collection

Study data were prospectively collected by research nurses at each site, using a data handling protocol (Appendix: **Supplemental Digital Content 4**). Guideline adherence

Table 1: Description of Implementation Strategies Used, According to Effective Practice and Organization of Care classification

Implementation Strategy	Intervention	Phase II	Phase III
Audit and feedback	Repeated evaluation of implementation process strategies used and level of perceived adherence to guideline recommendations	+[e]	+
Monitoring the performance of the delivery of healthcare	Posters with delirium screening adherence and delirium incidence	+	+
Educational materials	Reader development and dissemination; Interactive website e-learning (with instructional videos, e.g. on the use of screening instruments CAM-ICU[a] / ICDSC[b])	+	+
Educational meetings	Education of expert teams at each hospital / ICU[c] Education sessions	+	+
Educational outreach visits, or academic detailing	Interactive workshop sessions: Education about the severity and impact of delirium on patient outcomes on short and long term. The importance of why screening for delirium is important and what may work as preventive measures	+	+
Clinical Practice Guidelines	Construction of general delirium guideline protocol by several "consensus group"-meetings with representatives from each ICU (physicians, nurses). During the sessions, various local protocols (if any) from each ICU would be made visible when discussing the interpretation and translation of the guideline into a workable and widely endorsed protocol among participating centers.	-[**]	+
Inter-professional education	Spot-checks for screening were first done by expert-team members, but later by all nurses, checking and discussing each other's delirium assessments	+	-
Local consensus processes	Yes, see previous point under "Clinical Practice Guidelines"	-	+
Local opinion leaders	Medical and nursing stakeholders were recruited and involved in the study and its execution. They had the task to appeal to people, encouraging colleagues to work according to the guidelines (e.g. during daily rounds / visits) We appointed participating intensivists and nurses as local opinion-leaders.	+	+
Patient-mediated interventions	Family involvement was encouraged: • delirium information poster and info booklet placed in family room • Instructions by nurses to family members on participation in daily care and communication in case of delirium	-	+
Reminders	Operationalization of existing PDMS[e] for integration of delirium guideline protocol. Reminders for screening was preferentially incorporated. One of the hospitals did not have a digital PDMS system which hampered the implementation process.	+	+
Tailored interventions	Yes: based on pre-implementation assessment of barriers and facilitators	+	+

[a]CAM-ICU: Confusion Assessment Method for Intensive Care Unit; [b]ICDSC: Intensive Care Delirium Screening Checklist; [c]ICU: Intensive Care Unit; [d]PDMS: Patient Data Management System. [e]plus (+) and minus (-) -signs indicate whether individual implementation strategies were used during: the phase II or phase III (see: Figure 1).

was measured using seven performance indicators (Appendix: **Supplemental Digital Content 5**). During phase I, the presence of delirium was defined as: treatment with any anti-psychotic drug or documentation of a delirium diagnosis in the medical or nursing chart. During phases II and III, delirium was diagnosed with the CAM-ICU or ICDSC [20,21]. Coma was defined as a sedation level compatible with a Richmond Agitation-Sedation Scale (RASS) score [22] of -4 or -5 or a Ramsay Sedation Scale score [23] less than 5 or a Critically Ill Assessment (CIA) score [24] less than 7. A "delirium day" was defined as at least one recorded delirium diagnosis in a 24-hour period. A coma-day was defined as documented presence of coma with absence of documented delirium during a 24-hour period.

Statistical Analysis

Demographics are presented as numbers and percentages; medians and interquartile ranges; or means and standard deviations where appropriate. Differences in guideline adherence between the three phases, as expressed by crude numbers and percentages, were assessed with a χ^2 test. To examine between-group differences we used Kruskal-Wallis test for non-parametric analyses. Differences in clinical outcomes between the three phases were assessed with adjusted regression models. Poisson regression was used for count data (e.g. number of delirium assessments per day), logistic regression for binary outcomes, and linear regression for continuous outcomes. Guideline adherence and presence of brain dysfunction were analyzed on day level, with random effect models with a random intercept for patient. Duration of mechanical ventilation, ICU length-of-stay (LOS), ICU and hospital mortality were analyzed on patient level with fixed effect models. The adjusted models used severity of illness score (APACHE II), hospital, age and admission diagnosis (elective or acute surgery, versus medical diagnosis) as covariables. Differences between the periods were expressed as adjusted rate ratios (aRR), odds ratios (aOR) or betas. Missing baseline data were imputed using single imputation with the AregImpute function in R. Two-sided *P* values <0.05 were considered statistically significant. All analyses were performed with computer software programs R (extension packages: foreign, lme4, and rms) and IBM SPSS Statistics version 23.0.

RESULTS

In total 4,853 patients were admitted during the three data collection periods. As 923 patients had to be excluded (Appendix: **Supplemental Digital Content 6**), data of 3,930 patients, with a total of 18,288 patient-days, were analyzed. Demographics are presented in **Table 2**. The e-learning programs in phases II and III were completed by 90% (73/81) of physicians and 91% (374/409) of nurses.

Table 2: Patient Demographics and Baseline Clinical Characteristics

Characteristic	***Data-collection period***[a]		
	Phase I: Baseline	***Phase II: Screening Implementation***	***Phase III: Guideline Implementation***
No. of patients, n	1337	1399	1194
No. of ICU† days, n	6527	6086	5675
Gender, n (%)			
Male	775 (58)	789 (56)	710 (60)
Female	562 (42)	610 (44)	484 (40)
Age (years), median (IQR†)	66 (54; 75)	66 (53; 75)	65 (5; 74)
Admission status, n (%)			
Elective surgery	401 (30)	432 (31)	339 (28)
Emergency surgery	188 (14)	200 (14)	167 (14)
Medical	748 (56)	767 (55)	688 (58)
APACHE-II[b], median (IQR)	16 (11, 22)	15 (10, 21)	16 (11, 21)
Mechanically Ventilated patients, n (%)	560 (42)	541 (39)	593 (50)
Hospital, n (%)			
1	145 (11)	155 (11)	195 (16)
2	247 (19)	248 (18)	242 (20)
3	231 (17)	251 (18)	249 (18)
4	158 (12)	166 (12)	76 (6)
5	251 (19)	271 (19)	216 (18)
6	305 (23)	308 (22)	216 (18)

IQR = Interquartile Range, ICU = Intensive Care Unit.

[a] See Figure 1 for further explanation.

[b] Acute Physiology and Chronic Health Evaluation II range is 0-71.

Primary Outcomes - Guideline Adherence

Figure 2 and Appendix: **Supplemental Digital Content 7** show the crude performance indicator metrics presented as percentages. Delirium screening increased from 35% to 93% (P<0.001) to 96% (P<0.001). Continuous intravenous benzodiazepine sedation decreased from 36% to 31% (P<0.001) to 17% (P<0.001). Administration of daily intermittent benzodiazepines boluses had not consistently increased over the three phases. The amounts given (mean of 0.22-0.48 mg/day of diazepam equivalent; see legend of Supplemental Digital Content 7) seemed negligible compared with usual daily dosages of continuous intravenous benzodiazepines. While the daily use of midazolam, fentanyl and morphine had decreased, that of propofol, dexmedetomidine and remifentanil had increased (Appendix: **Supplemental Digital Content 8)**. Application of physical therapy (PT), early mobilization of patients, sedation assessments, and light sedation improved significantly. The medians of all available daily maximum RASS scores in mechanically

ventilated patients were significantly different between the study phases ($P<0.001$), indicating less deep sedation after the implementation (Appendix: **Supplemental Digital Content 9**).

Appendix: Supplemental Digital Content 10 shows the adjusted effect changes of the performance indicators. Implementation of delirium screening resulted in a significant improvement in adherence to delirium screening, sedation assessments, light sedation, less use of continuous intravenous benzodiazepine-sedation, and performing PT compared to the baseline period. These ORs indicate, for example, that for a random patient on a random admission day, the odds of getting sedated with continuous intravenous benzodiazepines was 0.5 (or 2 times smaller) after implementation of delirium screening. These improvements in adherences relative to the baseline period were maintained after implementation of the guideline. Early mobilization (as opposed to PT) only improved after guideline implementation but not after screening implementation. Guideline implementation resulted in additional improvements compared with the screening implementation phase for: delirium screening, use of benzodiazepines, performing PT, and performing early mobilization when feasible.

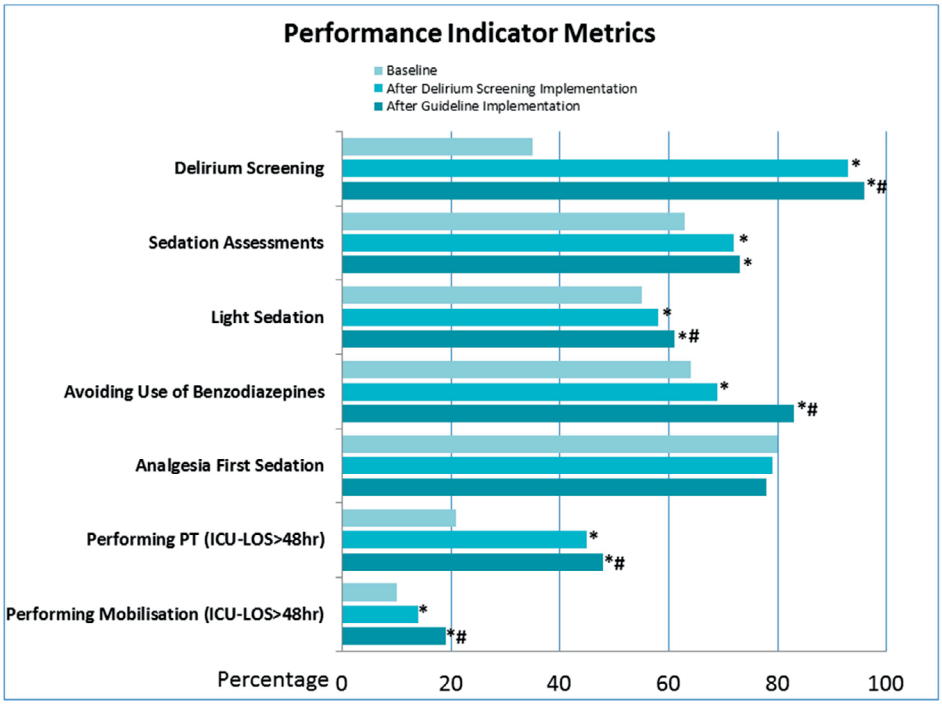

Figure 2: Adherence to Guideline Recommendations
This figure graph shows adherence percentage per performance indicator for the three data collection periods. See Supplemental Digital Content 7 for crude numbers. * Indicates a significant change relative to the baseline period. # Indicates a significant change after guideline implementation relative to the screening implementation period. For adjusted analyses: see Supplemental Digital Content 10.

Secondary outcomes - Clinical Outcomes

Table 3 shows crude and adjusted clinical outcomes changes per study phase. The duration of delirium decreased over three periods from 5.6 days to 2.9 days (Beta: **-2.6** days; 95% CI, -3.5 to -1.6 days; *P*<0.001); and to 3.3 days after guideline implementation (Beta: **-2.2** days; 95% CI, -3.2 to -1.3 days; *P*<0.001). Implementation of delirium screening resulted in 6% more patients detected with delirium in the third study period compared with the baseline period (OR **1.4;** 95% CI 1.2-1.7; *P*<0.001). Appendix: **Supplemental Digital Content 11** shows the cumulative proportions of delirium- and coma(-free) days as changes in percentages for the three study periods. In the adjusted analysis (Appendix: **Supplemental Digital Content 12**) only the coma-days were significantly reduced in phases II and III relative to phase I (from 14% to 12%; OR **0.6**; 95% CI, 0.4-0.8; *P*<0.001, and from 14% to 9%; OR **0.5**; 95%CI, 0.4-0.6; *P*<0.001). There were no significant changes for the other study outcomes.

DISCUSSION

In this study, the implementation of delirium monitoring and other elements of delirium care recommended in the 2013 PAD-guideline recommendations, was associated with modest, though significant, improvements in six of the seven studied care processes, corresponding with fewer delirium or coma days. On the assumption that the participating ICUs already applied light sedation practices in general, we decided *not* to focus strongly on safety screens for Spontaneous Awakening and Breathing Trials (SATs and SBTs), which may have precluded improvements of the secondary outcomes, such as length of ventilation, ICU stay or mortality.

We found that delirium screening resulted in slightly higher delirium detection rates, probably on account of the phenomenon that the use of a validated delirium screening tool increases the detection rate, especially of hypoactive delirium [25]. This may also explain that the cumulative number of delirium- and coma free days in the entire population did *not* decrease significantly in spite of decreased mean duration of delirium and days with coma per patient. Several previous studies on delirium screening implementation [26-29] and PAD-guidelines [7,30-32] also have reported improvement in delirium screening adherence. Further, a recent systematic review reported that adherence to delirium screening was assessed in in 15 of 21 implementation studies, thirteen of which found improved adherence, with rates ranging from 14% to 92% [6].

In a previous trial (SLEAP trial), SATs/SBTs did not have additional benefit for length of stay or mortality in settings with relatively light sedation practices [33]. The sedation levels we found (RASS -1 [IQR -3 - 0) more closely resembled those of patients in the SLEAP trial (RASS between -2 and -1) than those of patients in the ABC-trial (RASS between -4 and

Table 3: Secondary (clinical) outcomes

Outcomes	*Crude analysis*						**Adjusted[a] Effect Values**
	Phase I: Baseline		***Phase II: Screening Implementation***		***Phase III: Guideline Implementation***		***adjusted OR/RR/Beta[a](95%CI; P-value)*** ***a)Phase I vs. Phase II*** ***b) Phase I vs. Phase III*** ***c) Phase II vs. Phase III***
	Patients (n)		*Patients (n)*		*Patients (n)*		
Delirium duration (days), mean (SD)	274	5.6 (8.6)	300	2.9 (3.3)	319	3.3 (4.5)	a) -2.6 (-3.5 - -1.6; *P*<0.001) b) -2.2 (-3.2 - -1.3; *P*<0.001) c) 0.3 (-0.6 - 1.2; *P*=0.46)
Patients with delirium during ICU admission, n (%)	1337	274 (21%)	1399	300 (21%)	1194	319 (27%)	a) 1.2 (0.9 - 1.4; *P* =0.16) b) 1.4 (1.2 - 1.7; *P* <0.001) c) 1.2 (1.0 - 1.5; *P=0.*25)
Duration of mechanical ventilation (days), mean (SD)	560	4.6 (8.2)	541	4.9 (6.4)	593	4.7 (6.5)	a) 0.5 (-0.3 - 1.3; *P=0.*23) b) 0.4 (-0.4 - 1.2; *P*=0.36) c) -0.1 (-0.9 - 0.7; *P*=0.75)
ICU LOS (days), mean (SD)	1337	4.9 (6.9)	1399	4.3 (6.0)	1194	4.8 (5.9)	a) -0.3 (-0.8 - 0.1; *P*=0.19) b) -0.1 (-0.6 - 0.3; *P*=0.56) c) 0.2 (-0.3 - 0.6; *P*=0.49)
ICU Mortality, n (%)	1337	135 (10.1)	1399	140 (10.0)	1194	126 (10.6)	a) 1.3 (1.0 - 1.7; *P*=0.08) b) 1.3 (0.9 - 1.7; *P*=0.13) c) 1.0 (0.7 - 1.3; *P*=0.88)
Hospital Mortality, n (%)	1337	216 (16.2)	1399	226 (16.2)	1194	194 (16.2)	a) 1.3 (1.0 - 1.6; *P*=0.057) b) 1.1 (0.9 - 1.5; *P*=0.31) c) 0.9 (0.7 - 1.1; *P*=0.39)

ICU = Intensive Care Unit. LOS = Length of Stay.

[a] Differences are expressed as adjusted odds ratios (aOR) or adjusted rate ratios (aRR) with the Phase I: Baseline (for a and b) and Phase II: After screening implementation (for c) as the reference. Adjusted for: APACHE II; hospital; age; and admission type.

-1), which indeed found a positive effect on mortality [34]. On the other hand, the implementation studies by Balas et al [7,35], that bared many methodological similarities to our study, but was a single-center study, also had a mean RASS of -1 indicating light sedation rates, but still established lower length-of-mechanical ventilation, applying awakening and breathing trials. Our lack of focus on SATs and SBTs may also be illustrative for the tension between the premises of the PAD-guidelines (with moderate emphasis on SATs/SBTs), the ABCDE(F) concept (with strong emphasis) and more recent insights such as provided by the SLEAP study and as substantiated in the eCASH concept that has even questioned the value of daily sedation stops as opposed to goal-directed sedation [36]. Moreover, our results on patient outcomes are in line with a recent meta-analysis reporting that interventions that reduced delirium duration did not necessarily translate into reduced short-term mortality [37].

Implications of our findings

From an implementation perspective, we learned several lessons on evidence-to-practice translation. First, our implicit assumption that other improvements such as SATs and SBTs would follow next to our efforts to implement delirium-oriented measures, not specifically aimed at safety screens, has been falsified. Second, ICU teams less experienced with use of the guideline bundles or relying solely on "local champions" rather than interprofessional implementation teams should not try to implement all PAD/ABCDE bundle elements simultaneously within a limited time frame. Of note, our study deployed one or two local champions (intensivist or research nurse), but limited funding precluded appointment of full interprofessional teams (IPTs), existing of all relevant stakeholders, such as residents, respiratory therapists, physical therapists and other dedicated health care workers. Deploying such IPTs has been shown in other implementation studies to be essential for multi-bundle implementation within a limited timeframe [7,38,39]. A graded or phased implementation seems much more feasible in such relatively resource-limited settings and we learned that integration of bundle elements should not be confused with their simultaneous adoption. Third, not only the caregivers, but also the dedicated 'role models' have a learning curve for providing education and the feedback, so patience is of the essence. Fourth, successful implementation of bundle elements requires taking into account the baseline situation and contextual issues, such as existing barriers and facilitators, because many have been identified and not all are pertinent to all settings [40].

The strengths of our study include the prospective design, use of tailored multifaceted implementation strategies, the largest cohort to date outside of the United States, and the representative mix of ICU types supporting the translatability of our findings. Further, we deployed a pragmatic approach: implementation as part of daily clinical practice instead of deployment in a controlled research setting, which is also in contrast

to most published studies. Several limitations need to be addressed. First, the Hawthorne effect was not avoided, seeing that delirium screening implementation alone resulted in improved adherence to several guideline recommendations. Second, duration of delirium might be a doubtful outcome parameter due to the difference between a clinical diagnosis as assessed by chart review at baseline compared with the second and third phases (based on validated screening instruments). Long-term outcomes, such as cognition or post-traumatic stress disorder may be more relevant outcomes. Lastly, certain changes over time may have been overestimated in the presence of secular trends [41].

In conclusion, this largest pre-post implementation study outside of the US of delirium-oriented measures based on the 2013 PAD-guidelines showed that implementation had improved health professionals' adherence to delirium guidelines, which was linked to reduced brain dysfunction. Our data add to existing implementation literature due to the non-US setting, strongly enhancing translatability of findings. Furthermore, implementation lessons learned that are unique for our study pertain to: 1) the feasibility of staggered versus simultaneous implementation of bundle-elements, that seem strongly dependent on local resources (e.g. local champions, versus interprofessional implementation teams or level of previous experience with the guidelines), and: 2) the fact that our 'error of omission' of daily safety screens for SATs and SBTs may have precluded concurrently improved clinical outcomes, adding strong empirical support from a 'real-life setting' for effectiveness of individual ABCDE-bundle elements.

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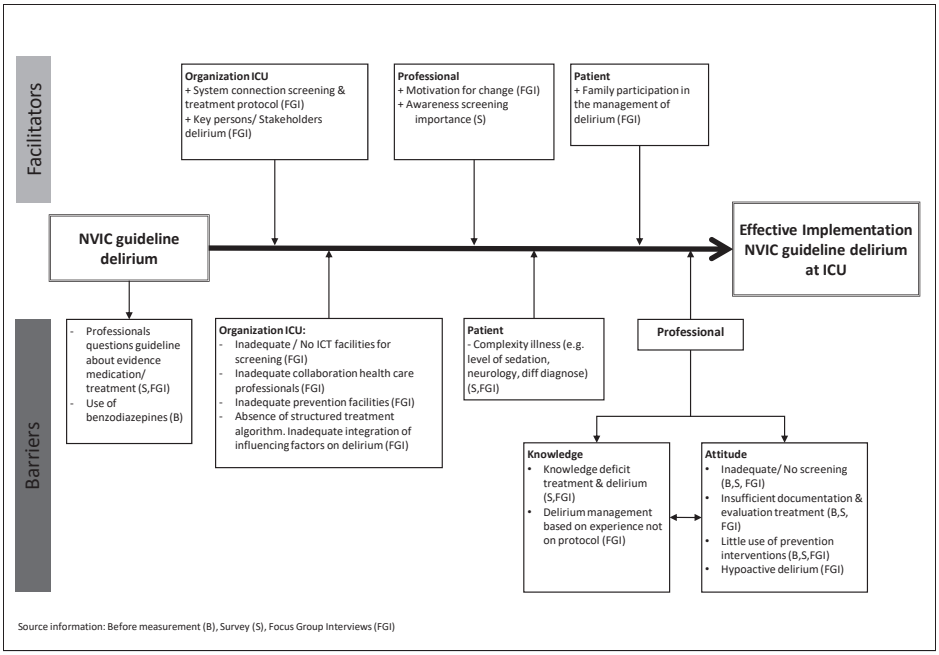
APPENDIX:



Supplemental Digital Content 1: Results Baseline analysis (compliance with guideline, facilitators and barriers)

Data about barriers and facilitators for implementation of guideline are presented below in the schematic way and more information about barriers found have previously been published by Trogrlic at al in 2016. (Reference: Trogrlic Z, Ista E, Ponssen HH, Schoonderbeek JF, Schreiner F, Verbrugge SJ, Dijkstra A, Bakker J, van der Jagt M. Attitudes, knowledge and practices concerning delirium: a survey among intensive care unit professionals. Nurs Crit Care 2016; 22: 133-140.)

Supplemental Digital Content 2: Theoretical substantiation of strategies

Theorie	Focus	Implementatie strategie
Social learning theory[1]	- Insert key figures / role models - Education	Education: - Modeling - Promoting self-efficacy - Identification
Social influence theory[2]**;** **Theorie of Leadership**	- Attitude change - Deployment of key figures / role models - Achieve consensus	- Use role models - Performance measurement / insight - Feedback - Consensus meetings
Theorie of Leadership[3]	- Leadership, coaching	- Encourage, motivate / support staff

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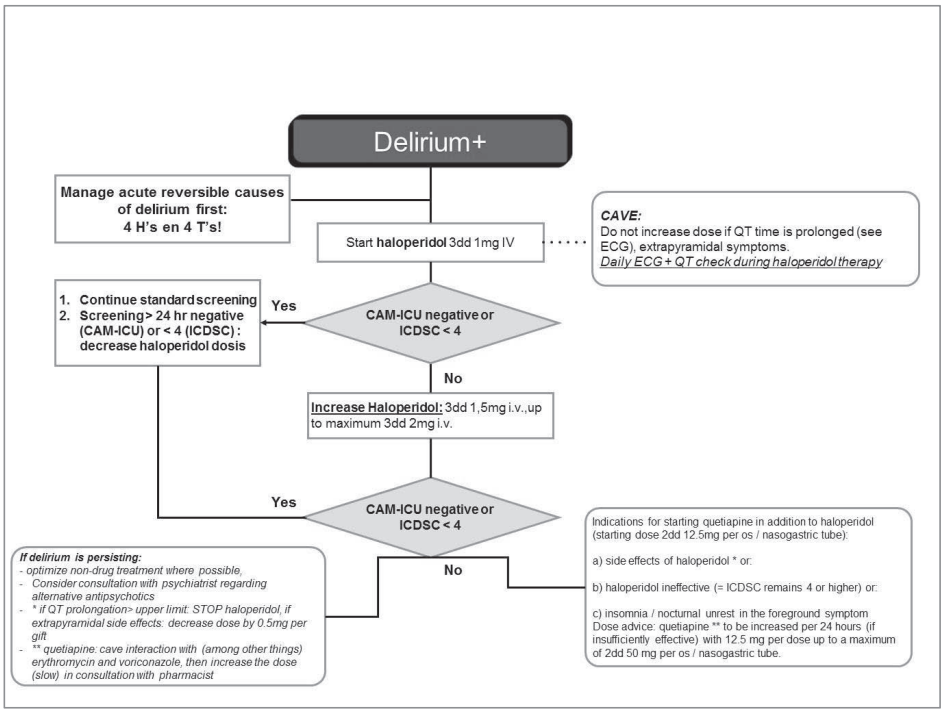
Supplemental Digital Content 3a: Daily Pain-Agitation-Delirium Care Goals Instructions



Supplemental Digital Content 3b: Flowchart antipsychotics

Supplemental Digital Content 4: Case Record Form (CRF) items for the iDECePTIvE study*
**Original CRF and data handling protocol are in Dutch and available upon request.*
Demographic
Age, Gender
Admission
Date of admission / date of discharge (Discharge to: Nursing Department, Medium care department, high care department, another ICU, another hospital, Elsewhere, Passed away)
On Admission (yes, no, not known): 1. Patient has aphasia, 2. Patient has mental disability, 3. Patient has language barrier (Dutch), 4. Patient has vision impairment (need glasses), 5. Patient has hearing impairment (hearing aid required)
Apache II, Admission status (medical, emergency surgery, elective surgery)
First 24 hours: Serum urea (highest) value, Metabolic acidosis? Is there infection? Total dose of Morphine (the first 24h)
Died during hospital admission
Daily variables during entire ICU stay
Use of haloperidol (mg), seroquel (quetiapine) (mg), olanzapine (zyprexa) (mg), another antipsychotic (mg), bolus benzodiazepines (mg)
Sedatives use per perfusion pump (for ≥2 hours / day) (yes or no): midazolam, lorazepam, propofol, clonidine, dexmedetomidine, other (specify)
Opiates use per perfusion pump (for ≥2 hours / day) (yes or no): morphine, fentanyl, remifentanil, other (specify)
Screening scales measures for: delirium (CAM-ICU or ICDSC), sedation (RASS, RAMSAY, CIA), pain (VAS, BPS, CPOT)
Renal dysfunction:
• CVVH has been applied to the patient today (yes / no)
• Creatinine (highest) (micromol/l)
• Diuresis (ml / day)
Mechanical ventilation (yes / no)
Delirium prevention (yes / no / not known / not applicable):
• Patient has had physiotherapy today
• Patient was mobilized
• Use of glasses
• Use of hearing aid
• Patient slept well last night (> 4h)
• Has the patient used earplugs?
• Patient was awakened by the staff
• Is a sleeping drug prescribed? If yes: which one? melatonin, benzodiazepines, other (specify)
• Patient was restricted due to delirium?
Patient is on the: open room or single box / room
When patient was delirious, did any adverse events occur (yes / no). If yes: what was the impact (no/ moderate/ serious):
• Patient has fallen out of bed / chair today
• Patient has removed his ET tube
• Patient has removed his nasogastric / duodenum tube
• Patient has removed his peripheral line
• Patient has removed his central line
• Patient has removed his arterial line
• Patient has removed his urinary catheter
• Patient has been removed .....drain
• Patient is aggressive

Data accuracy was ensured by the research coordinator (ZT) by checking a minimal of three CRFs of every ICU for each data collection period.

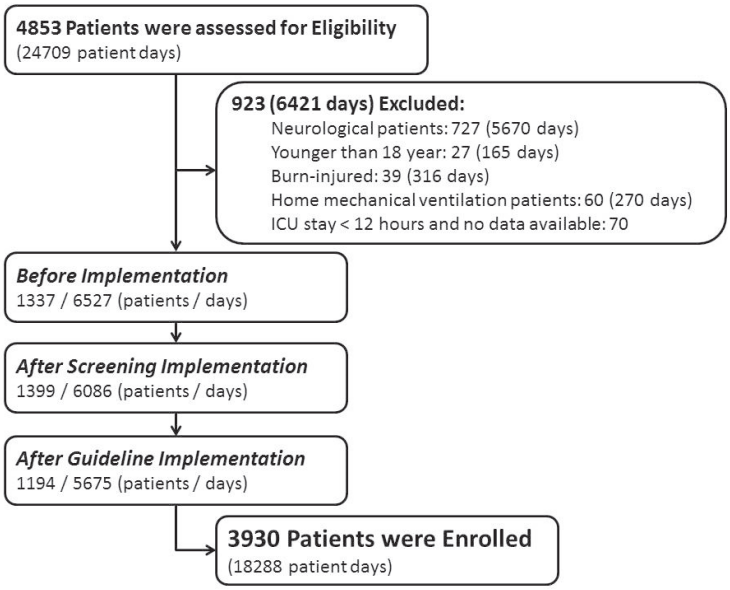
Supplemental Digital Content 5: Performance indicators assessing adherence to delirium guidelines recommendations (pertaining to delirium and based on the Pain, Agitation and Delirium guidelines)

Recommendation	Performance indicator	Indicator metric[a] %
Routine monitoring of delirium with CAM-ICU or the ICDSC should be done in all adult ICU patients	*1) Assessment of delirium with CAM-ICU or ICDSC*	*1) Total No. of CAM-ICU or ICDSC assessments / Total no. of patient-days on ICU*
Use a light target level of sedation in mechanically ventilated adult ICU patients	*2) % of sedation assessments* *3)* % of lightly sedated ventilated patients	*2) Total No. of days with at least one sedation assessment recorded / Total No. of patient-days on ICU* *3)* No. of light sedation days / Total No. of ICU days in mechanically ventilated (on one or more days) patients AND having received sedation and/or opioids *Light sedation level defined as:* • *Richmond Agitation and Sedation Scale (*RASS) *> -3 or* • *Ramsay score < 5 or* • Critically Ill Assessment Scale (CIA) *> 6*
Benzodiazepines should be avoided as routine sedative because its use may be a risk factor for the development of delirium	*4) The % of patients sedated with benzodiazepines*	*4)* No. of sedation days with benzodiazepines *(continuous IV, more than 2 hrs.)*[b] / Total No. of ICU days in mechanically ventilated (on one or more ICU days) patients AND having received sedation and/or opioids
Analgesia-first sedation should be used in mechanically ventilated adult ICU patients.	*5) The % of days on which sedatives were administered without standard analgesic medication (norm: 0%)*	*5) No. of patient no-analgesia if sedated days / Total number of patient sedation days*
Performing early PT or mobilization in adult ICU patients whenever feasible to reduce the incidence and duration of delirium by patients with more than 48 ICU-LOS.	*6) % of patients (with LOS>2 days) having received PT* *7) % of patients (with LOS >2 days) having received mobilization when feasible*	*6) No. of patients days with PT / Total No. of patient ICU days; included with LOS > 2 days* *7) No. of patients days with mobilization / Total No. of patient ICU days; included with LOS > 2 days*

CAM-ICU: Confusion Assessment Method for Intensive Care Unit; ICDSC: Intensive Care Delirium Screening Checklist; ICU: Intensive Care Unit; LOS: Length of Stay; PT: Physio Therapy; ICU: Intensive Care Unit.

[a]" numerator / denominator".

[b] Daily benzodiazepines intermittent bolus dose was also recorded and for comparison between study periods converted to diazepam equivalent according to benzo equivalence table at http://benzo.org.uk.



Supplemental Digital Content 6: Enrollment of patients

Supplemental Digital Content 7: Crude data on the Primary Outcome: Adherence to the guidelines assessed with Performance Indicators

Performance indicator	***Crude Analysis***			***P-value[a]***
	Phase I: Baseline	***Phase II: After Screening Implementation***	***Phase III: After Guideline Implementation***	***a)Phase I vs. Phase II b) Phase I vs. Phase III c) Phase II vs. Phase III***
Delirium screening [b]CAM-ICU or ICDSC assessments at least once a day / Total No. of patient-days at ICU	2284 / 6527 (0.35)	5660 / 6086 (0.93)	5431 / 5657 (0.96)	a) <0.001 b) <0.001 c) <0.001
Sedation assessments (Total No. of days with at least one sedation assessment recorded / Total No. of patient-days at ICU)	4131 / 6527 (0.63)	4389 / 6086 (0.72)	4143 / 5657 (0.73)	a) <0.001 b) <0.001 c) 0.281
Light sedation (No. of light sedation days[c] / Total No. of ICU days in ventilated patients receiving sedation and /or opioids)	1271 / 2324 (0.55)	1192 / 2050 (0.58)	1402 / 2282 (0.61)	a) 0.021 b) <0.001 c) 0.027
Use of benzodiazepines (No. of benzodiazepines[d] sedation days / Total no. of ICU days in once ventilated AND received sedation and or opioids)	835 / 2324 (0.36)	633 / 2050 (0.31)	384 / 2282 (0.17)	a) <0.001 b) <0.001 c) <0.001
Analgesia first sedation (No. of patient no-analgesia if sedated days / Total number of patient sedation days)	417 / 1935 (0.22)	356 / 1709 (0.21)	356 / 1805 (0.2)	a) 0.59 b) 0.17 c) 0.41
Performing PT (ICU-LOS >2days) (No. of patient-days with PT / Total No. of patient ICU days included with LOS > 2 days)	1013 / 4741 (0.21)	1837 / 4085 (0.45)	1928 / 4043 (0.48)	a) <0.001 b) <0.001 c) 0.014
Performing mobilisation when feasible (ICU-LOS >2days) (No. of patient-days with mobilization / Total No. of patient ICU days included with LOS > 2 days)	477 / 4741 (0.1)	583 / 4085 (0.14)	748 / 4043 (0.19)	a) <0.001 b) <0.001 c) <0.001

[a] P-values tested with $\chi 2$ test comparing: a) Phase I and Phase II; b) Phase I and Phase III; c) Phase II and Phase III

[b] "numerator / denominator".

[c] Definition of Light sedation: Richmond Agitation and Sedation Scale (RASS) >- 3 or Critically Ill Assessment Scale (CIA) >6 or Ramsay Sedation Scale <5.

[d] Benzodiazepines = midazolam and / or lorazepam as continuous intravenous sedative. Daily benzodiazepines intermittent bolus dose of all benzodiazepines were recorded and for comparison between study periods converted to 1 mg diazepam equivalent according to benzo equivalence table at http://benzo.org.uk; For conversion of diazepam to other benzodiazepines, 1mg diazepam = 1 mg bromazepam; or = 1.33 mg midazolam; or = 5 mg lorazepam; or = 0.3 mg oxazepam; or = 0.5 mg temazepam. Bolus doses diazepam equivalents differences (P < .001) were as follow: Phase I = total 3134 mg (0.48 mg/day); Phase II = total 1330 mg (0.22 mg/day); and Phase III = total 2008 mg (0.35 mg/day).

Supplemental Digital Content 8: Medication use during study

Type of Agent	***Phase I: Baseline*** (n days = 2324)	***Phase II: After Screening Implementation*** (n days = 2050)	***Phase III: After Guideline Implementation*** (n days = 2282)
Midazolam, n[a] (%)	807 (35)	633 (31)	383 (17)
Lorazepam, n (%)	30 (1)	0 (0)	1 (<1)
Propofol, n (%)	773 (33)	895 (44)	1103 (48)
Clonidine, n (%)	309 (13)	304 (15)	467 (21)
Dexmedetomidine, n (%)	0 (0)	40 (2)	117 (5)
Morphine, n (%)	485 (21)	378 (18)	191 (8)
Fentanyl, n (%)	211 (9)	142 (7)	83 (4)
Remifentanil, n (%)	1015 (44)	1039 (51)	1461 (64)
Sufentanyl, n (%)	436 (19)	43 (2)	313 (14)

[a] Number of days with use of medication *(continuous IV, more than 2 hrs. per day)* in mechanically ventilated (on one or more ICU days) patients.

Supplemental Digital Content 9: Richmond agitation-sedation scale (RASS) overview

Phase	**Selection 1[a]**		**Selection 2[a]**	
	RASS Median [IQR]	*p*-value[b]	RASS Median [IQR]	*p*-value[b]
Baseline (I)	-1 [-3 - 0]		-2 [-4 – 0]	
Screening Implementation (II)	0 [-3 - 0]		-1 [-4 – 0]	
Guideline Implementation (III)	0 [-2 - 0]		-1 [-3 – 0]	
Total (all phases)	-1 [-3 - 0]	*p*<0.001	-1 [-4 - 0]	*p*<0.001

[a]Selection 1: Median of all daily maximum RASS scores on all ICU treatment-days in patients with at least one day of mechanical ventilation during ICU stay (n= 12151; RASS missing or another sedation scale used = 3918 days); Selection 2: Median of all daily maximum RASS scores on all ICU treatment-days in patients with at least one day of mechanical ventilation during ICU stay AND having received sedation and/or opioids (n= 6656 days; RASS missing or another sedation scale used = 1833 days).
[b]Kruskal-Wallis test (non-parametric ANOVA).

Supplemental Digital Content 10: Primary Outcome (Adjusted): Adherence to the guidelines assessed with Performance Indicators

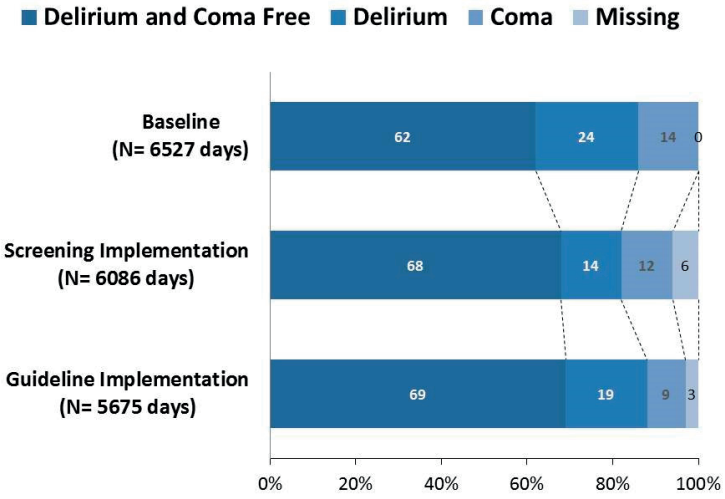
Performance Indicator	Adjusted[a] Effect Values adjusted OR/RR[a] (95%CI; *P*-value) **a)**[a]Screening Implementation vs Baseline **b)** Guideline Implementation vs Baseline **c)** Guideline Implementation vs Screening Implementation	Change		
		a)[a]	**b)**	**c)**
Delirium screening [b](Total No. of CAM-ICU or ICDSC assessments / Total No. of patient-days at ICU)	**a) 5.3** (4.9 - 5.7; *P*<0.001) **b) 5.8** (5.4 - 6.2; *P*<0.001) **c) 1.1** (1.0 - 1.2; *P*<0.001)	+[a]	+	+
Sedation assessments (Total No. of days with at least one sedation assessment recorded / Total No. of patient-days at ICU)	**a) 10.3** (7.3 - 14.4; *P*<0.001) **b) 5.7** (4.1 - 7.9; *P*<0.001) **c) 0.7** (0.5 - 1.0; *P*=0.069)	+	+	-[a]
Light sedation (No. of light sedation days[c] / Total No. of ICU days in ventilated patients receiving sedation and /or opioids)	**a) 1.3** (1.0 - 1.8; *P*=0.046) **b) 1.4** (1.1 - 1.9; *P*=0.012) **c) 1.1** (0.8 - 1.4; *P*=0.55)	+	+	-
Use of benzodiazepines (No. of benzodiazepines[d] sedation days / Total no. of ICU days in mechanically ventilated patients during at least one ICU-day AND having received sedation and/ or opioids)	**a) 0.5** (0.3 - 0.8; *P*=0.008) **b) 0.1** (0.1 - 0.2; *P*<0.001) **c) 0.2** (0.1 - 0.4; *P*<0.001)	+	+	+
Analgesia first sedation (No. of patient without-analgesia-while-sedated days / Total number of patient sedation days)	**a) 1.4** (0.9 - 2.3; *P*=0.18) **b) 1.2** (0.7 - 1.9; *P*=0.57) **c) 1.2** (0.7 - 2.0; *P*=0.53)	-	-	-
Performing PT (ICU-LOS >2days) (No. of patient-days with PT / Total No. of patient ICU days; included with LOS > 2 days)	**a) 3.9** (2.9 - 5.1; *P*<0.001) **b) 6.6** (5.0 - 8.8; *P*<0.001) **c) 1.7** (1.3 - 2.2; *P*<0.001)	+	+	+
Performing mobilisation when feasible (ICU-LOS >2days) (No. of patient-days with mobilization / Total No. of patient ICU days included with LOS > 2 days)	**a) 1.2** (0.9 - 1.6; *P*=0.31) **b) 2.1** (1.5 - 2.9; *P*<0.001) **c) 1.8** (1.4 - 2.5; *P*<0.001)	-	+	+

[a] Differences are expressed as adjusted odds ratios (aOR) or adjusted rate ratios (aRR) with either the "Baseline" phase (for a and b) or "Screening implementation" phase (for c) as the reference. Adjusted analyses included the following covariables: APACHE II; hospital; age; and admission type; plus (+) -sign indicates a significant change between a phase versus the reference; minus (-) -sign indicates no significant change between a phase versus the reference.

[b]" numerator / denominator".

[c] Definition of Light sedation: Richmond Agitation and Sedation Scale (RASS) >- 3 or Critically Ill Assessment Scale (CIA) >6 or Ramsay Sedation Scale <5, see manuscript text for references.

[d] Benzodiazepines = midazolam and / or lorazepam as continuous intravenous sedative.



Supplemental Digital Content 11: Proportion of patient-days with brain dysfunction (delirium or coma) Days shown are proportions of cumulative patient-days presenting the differences on delirium outcomes (Delirium and Coma Free Days; Delirium; and Coma) during the study phases. A small proportion of patient-day data pertaining to delirium or coma was missing due to non-adherence to delirium or sedation screening during the screening and guideline implementation phases. Adjusted analyses are shown in Supplemental Table 6 (Supplemental Digital Content 9).

Supplemental Digital Content 12: Adjusted Effect values of Proportion of patient-days with brain dysfunction (delirium or coma)

	Adjusted Effect Values (OR/RR; 95% CI; *P*-value)[a]		
	Screening Implementation vs Baseline	**Guideline Implementation vs Baseline**	**Guideline Implementation vs Screening Implementation**
Delirium- and Comafree Days	1.0 (95% CI, 0.8-1.3; *P*=0.8)	1.0 (95% CI, 0.8-1.3; *P*=0.83)	1.0 (95% CI, 0.8-1.2; *P*=0.73)
Delirium	0.9 (95% CI, 0.7-1.2; *P*=0.44)	1.2 (95% CI, 0.9-1.6; *P*= 0.28)	1.3 (95% CI, 0.9-1.7; *P*= 0.12)
Coma	**0.6** (95% CI, 0.4-0.8; *P*<0.001)	**0.5** (95% CI, 0.4-0.6; *P*<0.001)	0.8 (95% CI, 0.6-1.1; *P*=0.24)

[a] To examine the effect of the implementation on delirium outcomes (Delirium- and Coma-free Days; Delirium; and Coma), a logistic regression on day level, with random effect models, was used accounting for the repeated measures in the same patient with a random intercept for patient. A small proportion of patient-days with missing data on delirium or coma scales (due to non-adherence to delirium or sedation screening) were excluded from analysis.