4-24-2020

Impact of Early Mobility of ABCDEF Bundle on Delirium

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DOES IMPLEMENTING EARLY MOBILITY OF THE ABCDEF BUNDLE IMPACT DELIRIUM?
A SYSTEMATIC REVIEW

by

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A Major Paper Submitted in Partial Fulfillment

of the Requirements for the Degree of

Master of Science in Nursing

in

The School of Nursing

Rhode Island College

2020

Acknowledgements

I would like to thank Dr. Linda Dame DNP whose encouragement and guidance allowed me to grow as a researcher and professionally during the process of this systematic review. I would like to thank my readers, colleagues, and peers who supported me in making this final product. Finally, I owe my deepest gratitude to my husband Justin, without him this journey in advanced practice would not have been possible. To Mom, In Your Loving Memory, we did it.

Abstract

Delirium is an acute disturbance characterized by a fluctuating course of cognitive functioning and inattention which renders a patient's ability to receive, process, store, and recall information impaired. Delerium is part of a syndrome called Post-Intensive Care Syndrome and which consists of cognitive, physical, and psychiatric disturbances. Due to the magnitude of patients admitted to critical care suffering from such impairments, the Society of Critical Care Medicine formulated the ABCDEF bundle, a multidisciplinary approach composed of interventions to combat the incidence and prevalence of PICS and consists of: **A**ssess, prevent and manage pain, **B**oth spontaneous awakening and spontaneous breathing trials, **C**hoice of analgesia and sedation, **D**elirium monitoring and management, **E**arly mobility in the ICU, and **F**amily empowerment and engagement. The purpose of this project was to conduct a systematic review to determine if implementing the early mobility component of the ABCDEF bundle impacts delirium. By identifying interventions that decrease delirium, reduction of related long-term consequences associated would result. The PRISMA framework guided the selection of articles in this systematic review. A critical appraisal and cross analysis comparing the similarities and differences was conducted. Findings suggested that early mobility impacts the duration of delirium in critical care. Utilization of early mobility, as part of the ABCDEF bundle, should be considered as part of routine care in the critical care areas to decrease the prevalence of delirium.

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Does Implementing Early Mobility of the ABCDEF Bundle Impact Delirium Associated with Post-Intensive Care Syndrome?

A Systematic Review

Background/Statement of the Problem

A large majority of the expected five million admissions to the Intensive Care Unit (ICU) in the United States (U.S.) will survive. Advances in medicine have made it possible to effectively resuscitate, manage, and rehabilitate patients by means of a skilled multidisciplinary team, hemodynamic monitors, invasive lines, ventilator support, and various medication regimens. However, research has suggested that survivors can acquire a syndrome of cognitive, psychiatric, and physical impairments secondary to admission to the ICU termed Post-Intensive Care Syndrome (PICS) (Mikkelsen, Netzer, & Iwashyna, 2019).

Post-Intensive Care Syndrome is defined as the "remaining disability in cognition, psychological health, and physical health of the survivor of the intensive care unit" (Rawal, Yadav, & Humar, 2017, p. 90). Such impairments reflected in PICS refer to impaired thinking and judgment (cognition), psychiatric disorders such as post-traumatic stress disorder, depression and anxiety (psychiatric), and neuromuscular weakness (physical). Lone et al. (2016) conducted an international study in Scotland and identified that patients admitted to the ICU had over 50% higher mean hospital costs five years after discharge from the ICU than those who were not. The researchers propose this is due to the impaired cognitive, physical, and psychiatric functioning of PICS (Lone et al., 2016). Although PICS prevalence is unknown, the incidence of this chronic syndrome is not only a burden to the patient and their family but to the healthcare system as well.

In order to understand the magnitude of this syndrome, it is important to first understand the specific cognitive, psychiatric, and physical impairments that prompt PICS, which have been effectively measured in a number of studies. Due to the magnitude of those affected by PICS, measures have been instituted to reduce the incidence of PICS and one measure is the ABCDEF bundle. The ABCDEF bundle, created by the Society of Critical Care Medicine (SCCM), began the ICU Liberation initiative in the U.S. in an attempt to improve patient quality of life and address the various impairments of PICS. The ABCDEF bundle is composed of multidisciplinary interventions that symbolizes "**A**ssess, prevent and manage pain, **B**reathing Trials with daily sedative interruption and ventilator liberation practices, **C**hoice of sedation, **D**elirium monitoring and management, **E**arly mobility in the ICU, and **F**amily empowerment and engagement" (Marra, Ely, Pandharipande, & Patel 2017, p. 1).

As previously mentioned, the three realms of impairment affect the patient cognitively as well as the patient's mental health and physical ability. In regards to cognition, studies have revealed that there is not only a high incidence of impairment, but the impairment, ranging from mild to severe, has been shown to persist patients a year after discharge from the ICU. The cognitive impairment of delirium included in PICS has been linked to increased mortality and morbidity among patients in the ICU. The culture of bedrest and immobility commonly experienced in the ICU has been found to not only impact duration of mechanical ventilation and the development of ICU-acquired weakness, but also onset and duration of delirium. Therefore, the purpose of this project will be to conduct a systematic review in order to determine if implementing the early mobility component of the ABCDEF bundle impacts delirium.

Literature Review

Primary databases searched were CINAHL Plus with full text, Cochrane, UpToDate, Google Scholar, and PubMed. Key words used were intensive care unit, ICU syndromes including delirium, critical illness polyneuropathy, and post-traumatic stress disorders, mechanical ventilation, long-term complications of critical illness, Post-Intensive Care Syndrome, Post-Intensive Care Syndrome and prevention, as well as the ABCDEF bundle. Terms were searched separately and combined to generate results. Articles were initially limited to less than five years, but due to duration of the issue of PICS the period was expanded to thirty years (1989-2019).

Intensive Care Unit

As defined the by Department of Health in Australia, an ICU provides critical and life-sustaining measures to those who are acutely-ill and injured. The population and acuity of those in the ICU range from scheduled post-operative admissions to the critically-ill requiring mechanical ventilation. The population in each hospital's ICUs may vary depending on patient's medical conditions or surgical procedures performed. The group of providers including highly skilled nursing staff, medical doctors, physical therapists, and other skilled professionals make up the multidisciplinary team that provides direct patient and family care from admission to discharge from the ICU (Department of Health – Western Australia, n.d.).

Intensive Care Unit Syndromes

Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD) is characterized as "a severe stress response secondary to experiencing previous trauma" (Grossman & Porth, 2014, p. 212).

Post-Traumatic Stress disorder is characterized by three states: intrusion; avoidance; and hyperarousal. Intrusion, or "flashbacks" during daytime hours or nightmares during sleep are the most common symptoms associated with the disorder; avoidance refers to the "emotional numbing" that occurs associated with the trauma; and hyperarousal refers to the "presence of increased irritability, difficulty concentrating, exaggerated startle reflex, and hypervigilance" (Grossman & Porth, 2014, p. 213).

A study by Patel et al. (2016) found that of the 255 survivors of the ICU, 181 were found to have ICU-related PTSD at three months and 160 subjects were found to have ICU-related PTSD at 12-month follow-up. Patients were assessed either by the PTSD Checklist Event-Specific Version (score ≥ 50) or item mapping using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and a high probability of PTSD was noted using both diagnostic tools in this study.

Depression and Anxiety

In a study conducted by Wunsch et al. (2014), one percent of the over 24,000 patients who received mechanical ventilation had a new psychiatric disorder. The psychiatric disorders that patients were diagnosed with were anxiety and depression. The study further proposed that 19% of patients received one or more prescriptions for psychoactive medications. The most common symptoms of anxiety include excessive worry, irritability, restlessness, and fatigue. Patients with symptoms of depression may complain of fatigue, loss of interest, poor appetite, sense of hopelessness, and insomnia (Van Amerigen, 2019). In the study by Pandharipande et al. (2013), it was found that 37% of survivors experienced depression. With depression, patients also experienced associated somatic complaints such as pain (Wunsch et al., 2014)

Critical-Illness Polyneuropathy

According to Sander, Golden, and Danon (2002), critical illness polyneuropathy appears to be a common complication of severe sepsis. A correlation has been found to exist between glucose dysregulation and low serum albumin levels in critical illness. The cause of axonal injury, which causes polyneuropathy, is unknown but various studies suggest impairment of microcirculation of distal nerves causing ischemia and axonal degeneration (Bolton, Bryan, & Zochodone, 1993; Latronico, Peli, & Botteri, 2005). In an international study performed in France in 2002, neuromuscular weakness due to critical illness myopathy (CIM) or critical illness polyneuropathy (CIP) was noted in 25% of patients who were mechanically ventilated in the ICU for at least seven days even when daily awakening trials were performed with a median duration of 21 days (Jonghe et al., 2002).

In the study by Pandharipande et al. (2013), over 30% of ICU survivors were disabled physically in their activities of daily living with 26% being disabled in instrumental activities of daily living. Persistence of such disability was noted one year after discharge. An international study performed by Griffiths et al. (2013) was conducted and included 293 patients who spent greater than 48 hours in the ICU. Twenty-two ICUs were included and post-ICU discharge follow up was obtained at six and 12 months. At six-month follow-up, 25% of patients reported needing assistance with care and 22% needed assistance at 12 months. Over three quarters of the care received was provided by family caregivers at the six-month and 12-month follow up (Griffiths et al., 2013). Participants in this study also alluded to the negative impacts on employment not only to the patient but the family as well. Mobility problems impacted

over half of the individuals at six months post discharge. In addition, almost three-fourths of the individuals reported moderate or severe pain at 12-months post-discharge related to their hospitalization (Griffiths et al., 2013).

Neuromuscular Weakness

Neuromuscular weakness in the ICU is most often due to critical illness myopathy, critical illness polyneuropathy, or both. Stevens et al. (2009) utilized the term "intensive care unit-acquired weakness (ICUAW)" for patients who have idiopathic clinically detected weakness post critical illness. Price, Mikkelsen, Umscheid, and Armstrong (2016) suggested a clinically significant association with neuromuscular blocking agents and residual neuromuscular dysfunction with critical illness.

Delirium

Delirium is defined by the Journal of the American Medical Association as “a disturbance of consciousness characterized by an acute onset and fluctuating course of impaired cognitive functioning so that a patient's ability to receive, process, store, and recall information is strikingly impaired” (Ely et al., 2001, p. 2703). According to the New England Journal of Medicine, close to a quarter of survivors of the ICU experienced cognitive impairment (Pandharipande et al., 2013). Pandharipande et al. (2013) conducted a multicenter study in which patients were admitted to the medical or surgical ICU with respiratory failure, cardiogenic shock, or septic shock. The purpose was to evaluate the prevalence of chronic cognitive deficits post admission to the ICU. Pandharipande et al.’s hypothesis was that the longer a patient suffered from delirium and the more sedative and analgesic agents a patient received during hospitalization, the more severe the cognitive impairment would be. Certified evaluators utilized the Clinical

Dementia Rating (CDR) Scale to evaluate for the presence of dementia in patients for part of the study. Scores ranged from 0 to 3.0 and a higher the score the more severe dementia. Patients with a CDR score greater than 2.0 were not included in the study (Pandharipande et al., 2013). In this study, the presence of delirium as well as the medications utilized, such as sedatives or analgesics administered, were examined. Delirium was assessed with the use of the Confusion Assessment Method for the ICU (CAM-ICU). This algorithm assesses for the presence or absence of delirium on the basis of an acute change or a fluctuation in mental status, inattention, disorganized thinking, and altered level of consciousness. If an individual was found to have delirium based on this algorithm, the patient would be classified as CAM-ICU positive, while the lack of delirium classified the patient as CAM-ICU negative. Level of consciousness was assessed with the use of the Richmond Agitation–Sedation Scale (RASS), in which scores range from -5 – 4 (Appendix A). Higher scores indicated more agitation, 0 indicated an alert and calm state, while -5 indicated a coma or unarousable state (Pandharipande et al., 2013). In addition, 448 of the 569 surviving patients underwent cognitive testing three months after discharge as some were now deceased and 382 of the 510 surviving patients were assessed 12 months after discharge. At the three month and twelve-month date, psychology professionals, who were unfamiliar regarding the patient's hospital course, assessed patients' cognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a tool used for evaluation of global cognition, including immediate and delayed memory, attention, visuospatial construction, and language (Pandharipande et al., 2013). Scores ranged from 40 to 160; a lower score indicated worse performance and cognition exhibited by a patient. Six percent of

individuals admitted to the medical or surgical ICUs had baseline cognitive deficits. However, three months post discharge patients presented with RBANS scores similar to that of a "moderate traumatic brain injury." Pandharipande et al. (2013) found 26% of patients presented with cognitive delays with scores that were reflective of mild dementia. Long-term cognitive scores were correlated with longer duration of delirium. Sedative medications including propofol, dexmedetomidine, and opiates, were examined and were not consistently associated with impaired or improved cognition. Such deficits were noted 12 months post discharge revealing cognitive deficits persisted in most patients (Pandharipande et al., 2013).

Post-Intensive Care Syndrome (PICS)

Post-Intensive Care Syndrome (PICS) is defined as the "remaining disability in cognition, psychological health, and physical health of the survivor of the intensive care unit" (Rawal et al. 2017, p. 90). Such impairments reflected in PICS refer to impaired thinking and judgment (cognition), psychiatric disorders namely post-traumatic stress disorder, depression and anxiety (psychiatric), and neuromuscular weakness (physical). Such impairments can persist months after discharge from the ICU. Patients with PICS do not present with the same symptoms, as each patient experiences a varying level of impairment in some or all of the areas mentioned. One of the greatest predictors of long-term cognitive impairment post-intensive care stay, as suggested by Pandharipande et al. (2013) was the presence of delirium. According to Fernandes, Jaeger, and Chow (2019), factors that increased the risk of developing PICS included prolonged ICU stay and prolonged mechanical ventilation. Other diseases and medication related factors included

delirium, blood glucose mismanagement, sepsis, uncontrolled pain, and inappropriate sedation (Fernandes et al., 2019).

ABCDEF Bundle

The SCCM in the Pain, Agitation, and Delirium (PAD) guidelines of 2013, recommended the following: routinely monitor all intensive care unit patients for pain, depth of sedation, and delirium using valid PAD assessment tools; assess and treat pain first before sedating patients; avoid deeply sedating patients; use non-pharmacological delirium management strategies over medications to prevent and treat ICU delirium; and link PAD management to ventilation weaning and early mobility efforts (Barr et al., 2013). These recommended guidelines are reflected in the multidisciplinary approach called the ABCDEF bundle. This multidisciplinary approach includes respiratory therapists, nursing, physicians, and rehabilitation specialists such as physical and occupational therapy. The ABCDEF bundle is composed of interventions that symbolizes **A**ssess, prevent and manage pain, **B**oth spontaneous awakening and spontaneous breathing trials (including sedation interruption, see Appendix B), **C**hoice of analgesia and sedation, **D**elirium monitoring and management, **E**arly mobility in the ICU, and **F**amily empowerment and engagement (Balas et al., 2019, p. 48). As suggested by Balas et al., the integration of pain management, sedation interruption, and delirium assessment with regular ventilator weaning trials and early mobility of the ICU population allowed for standardization of ICU care.

Assessment, prevention, and management of pain in the ICU population has been associated with patient specific outcomes such as a decrease in days requiring mechanical

ventilation. Prudent use of opioids is recommended due to the correlation of opioid misuse and delirium. Regular and routine protocols for pain assessment and re-assessment are encouraged by the SCCM in the pain, agitation, and delirium (PAD) guidelines of 2013 (Barr et al., 2013). One of the recognized scales to assess pain in the mechanically ventilated as well as the nonverbal patient is the Critical Care Pain Observation Tool. The Critical Care Pain Observational Tool uses objective information such as ventilator compliance, muscle tension, and facial expression to quantify a patient's pain score at rest and with repositioning. Spontaneous breathing trials coordinated with daily sedation interruption reflects the patient's readiness to commence the weaning process from the mechanical ventilator. Safe and effective measurements of readiness to wean have been proven to result in a decrease in average ventilator days as well as a decline in ICU acquired delirium. Another benefit to this interruption in sedation is that it prohibits excessive sedation. Prolonged immobility in the ICU leads to further muscular and respiratory deconditioning and weakness. "Early" mobility refers to the initiation of physical therapy, from passive range of motion to ambulation on the ventilator, as soon as the patient is hemodynamically stable (Fernandes et al., 2019; Kram, Dibartolo, Hinderer, & Jones, 2015).

Early Mobility

Early Mobility has been commonly accepted as "appropriate mobilization within two to five days of critical illness or injury" (Zhang, Zhang, Cui, Hong, & Zhang, 2018, p. 2). Such mobilization started as soon as stabilization of the critical illness has occurred is based on hemodynamic and assessment criteria. Criteria that would exclude a patient from early mobility initiation or continuation include: hemodynamic instability including

mean arterial pressure less than 65 mm Hg or more than 110 mm Hg; systolic blood pressure greater than 200 mm Hg, heart rate less than 40 beats per minute or greater than 130 beats per minute; respiratory rate less than 5 breaths per minute or more than 40 breaths per minute, as well as pulse oximetry less than 88%. Other contraindications to early mobility include increased intracranial pressure; active gastrointestinal blood loss; active myocardial infarction; continuing procedures such as continuous renal replacement therapy; patient agitation involving increasing sedation requirements; and an unsecured airway (Schweickert et al., 2009). Once early mobilization has been deemed safe, interventions ranging from passive range of motion to ambulation with a portable ventilator as tolerated are initiated with the assistance of the healthcare team and involves physical therapy, respiratory therapy, and nursing. Each patient is assessed daily for readiness for early mobility and is usually paired with daily sedation vacations and spontaneous breathing trials. Such cessation of sedation has been theorized to decrease serum concentrations allowing for a decreased risk of over sedation.

ABCDEF Bundle and PICS

Pun et al. (2019) implemented the ABCDEF bundle in over 15,000 adult ICU patients to reduce PICS. The authors included 68 ICUs and collected data on patients while implementing the ABCDEF bundle. The ICUs ranged from academic centers to community and federal hospitals and patients had a minimum of a one-day stay in the ICU. Pun et al. correlated complete utilization of the ABCDEF bundle and partial utilization with patient outcomes. The ABCDEF bundle was measured and included three set outcomes: patient-related, symptom-related, and system-related. Patient-related included mortality, ICU, and hospital discharge. Symptom-related included mechanical

ventilation, coma, delirium, pain, and restraint use. System-related focused solely on readmission to the ICU and discharge destination either home or another setting. A study by Kalfon et al. (2019) utilized the same program and noted a reduced prevalence of PTSD symptoms at one year, which was not measured by Pun et al. (2019).

Pun et al. (2019) concluded that the use of the complete bundle was associated with a decreased incidence of next-day mechanical ventilation, coma, delirium, physical restraint use, ICU readmission, and discharge to another facility other than home. According to the authors, there was a consistent dose-response relationship between implementation of the ABCDEF bundle and previously mentioned patient-related, symptom-related, and system-related outcomes. Pun et al.'s findings indicated that patient outcomes were improved when more components of the bundle were implemented (p <0.002).

Early Mobility and PICS

Early mobilization in the ICU has been suggested to be a safe way to impact not only physical but cognitive impairment as well. In a randomized control trial by Schweickert et al. (2009), ICU acquired weakness occurred less in the intervention group who received early physical therapy and mobility than in the control group who received standard care. The study also validated their primary outcome of independent functional status at discharge and this was achieved in over 50% of those in the intervention group versus 35% in the control group (Schweickert et al., 2009). Parker, Sirachroenachi, & Needham (2013) evaluated safety and patient outcomes and suggested that early rehabilitation interventions should be considered to address the acute and chronic impairments associated with PICS (Parker et al., 2013).

Early Mobility and Delirium

According to the American Association of Critical Care Nurses in 2016, evidence (level B) suggested that nurses should encourage early mobility to help prevent delirium related to increased immobilization. This iatrogenic risk factor is modifiable and dependent on appropriate assessment and identification of candidates for early mobilization in the ICU. A randomized controlled trial by Schweickert et al. (2009) as well as a quality improvement study by Needham et al. (2010) suggested that such early mobility could decrease delirium duration by two full days. Healthcare providers must also acknowledge that some unmodifiable risk factors can predispose a patient to delirium in critical illness and include hypoxemia or advanced age. Although the patient will be predisposed and likely develop delirium, early mobility has been proven to decrease the duration of delirium, which correlates directly with patient outcomes.

Theoretical Framework

A systematic review is a "review of a clearly formulated question that utilizes systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (Moher, Liberati, Tetzlaff, & Altman, 2009, p.264). A systematic review is incredibly important in the development of practice guidelines, as well as succinctly reporting data gathered to help better understand and utilize clinical evidence. The theoretical framework utilized for this systematic review was the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statement.

Moher and colleagues created the PRSIMA statement in order to allow for "improved reporting in systematic reviews" (Moher et al., 2009, p.265). Prior to PRISMA, aside from the Cochraine review, only 10 percent of those who performed systematic reviews utilized a protocol. Reviewing information systematically will allow for transparency in order to understand the reasoning for including or excluding studies in a systematic review (Moher et al., 2009).

The PRISMA flow diagram (Appendix C) includes five distinct phases of the collection and selection of randomized control trials for the creation of a systematic review. The four phases highlighted in the PRISMA flow diagram include identification, screening, eligibility, and inclusion. As the reader continues to follow the flow diagram, it will be evident which studies were excluded based on the author's inclusion and exclusion criteria. Finally, the number of studies utilized in the systematic review is noted adjacent to the included heading in the flow diagram.

The PRISMA statement consists of a 27-part checklist of items necessary to include when performing a systematic review. The PRISMA Statement was utilized to aid this author in formulating this systematic review. PRISMA by intention accurately evaluates interventions, but does not appraise the quality of the systematic review. Therefore, the Critical Appraisal Skills Programme (CASP) instrument was used as well. The CASP evaluated the strengths and weaknesses of each randomized controlled trial and allowed the author to evaluate the clinical significance of the research findings (Moher et al., 2009).

Method

Purpose

The purpose of this project was to conduct a systematic review in order to determine if implementing the early mobility component of the ABCDEF bundle impacts delirium. The research question investigated was: Does implementing Early Mobility of ABCDEF bundle impact onset or duration of delirium?

Inclusion / Exclusion Criteria

Inclusion criteria consisted of randomized controlled trials within the last fifteen years, written in the English language and studies which included the following: adult patients (over the age of eighteen), admitted to the ICU or specialty critical care units, measurement of delirium, and early mobilization of the ABCDE bundle (E).

Exclusion criteria included randomized controlled or clinical trials not written in the English language, and studies that included patients under the age of eighteen.

Search Strategy

The PRISMA checklist and flow diagram were used to guide the search strategy. The databases used for the literature search were Cinahl, PubMed, Google Scholar, and Medline. An initial search for "post-intensive care syndrome" was conducted utilizing the previously mentioned databases. Including and combining the terms "prevention" and "ABCDEF bundle and early mobility" further narrowed the search. The search included randomized control trials from January 2004 to May 2019. Each article was reviewed and determined if it met inclusion and exclusion criteria and the purpose of this systematic review.

Data Collection and Synthesis

Articles that met the inclusion and exclusion criteria were reviewed and information from each study transferred into two data collection tables created by this author. Table one consisted of the design, purpose of the study, setting, and sample population. Table two included outcome variables, as well as the results and limitations of each study. The creation of data collection tables aided the author in organizing and reviewing information.

Table 1. Data Collection

Design	Purpose	Setting	Population

Table 2. Data Collection

Outcome Variables	Results	Limitations

Critical Appraisal Tool

The Critical Appraisal Skills Programme (CASP) instrument, developed by the Public Health Resource Unit of the National Health Service in collaboration with the U.K. Centre for Evidence Based Medicine and the Birmingham critical appraisal skills program was utilized to critically appraise each RCT. The 11-question instrument evaluates the validity, results of the trial, and the applicability of the randomized control trial to current practice (Appendix D). Each appraisal question was answered to the best of this author's ability in order to assess the validity of the research included in this

systematic review (Public Health Resource Unit, Critical Appraisal Skills Program, 2009).

Cross Analysis

After data collection and the critical appraisal of the randomized controlled trials, data was analyzed to compare the similarities and difference across studies. A table was created to organize data regarding early mobility and its impact on delirium in the cross study analysis. In addition, how each study measured delirium and time interval (days, weeks, months, years) were included (table 3).

Table 3. Cross Study Analysis

Author	Early Mobility	Effect on Delirium	Measure of Delirium	Time Measured (days, weeks, months, years)

Results

Data Collection

The PRISMA flow diagram was utilized in order to identify appropriate literature. Databases were utilized in order to identify pertinent studies. An initial search included "early mobility." Search results showed 2,108 results in Cinahl, 14,291 in PubMed, 3,940,000 in Google Scholar, and 9,682 through Medline. The search was then narrowed by adding the term, "Intensive Care Unit." Search results showed 261 results in Cinahl, 328 in PubMed, 33,000 in Google Scholar, and 313 through Medline. The search was further narrowed by the additional term of "delirium." The resulting studies were then screened based on inclusion and exclusion criteria. Five studies were then chosen for review (Figure 1).

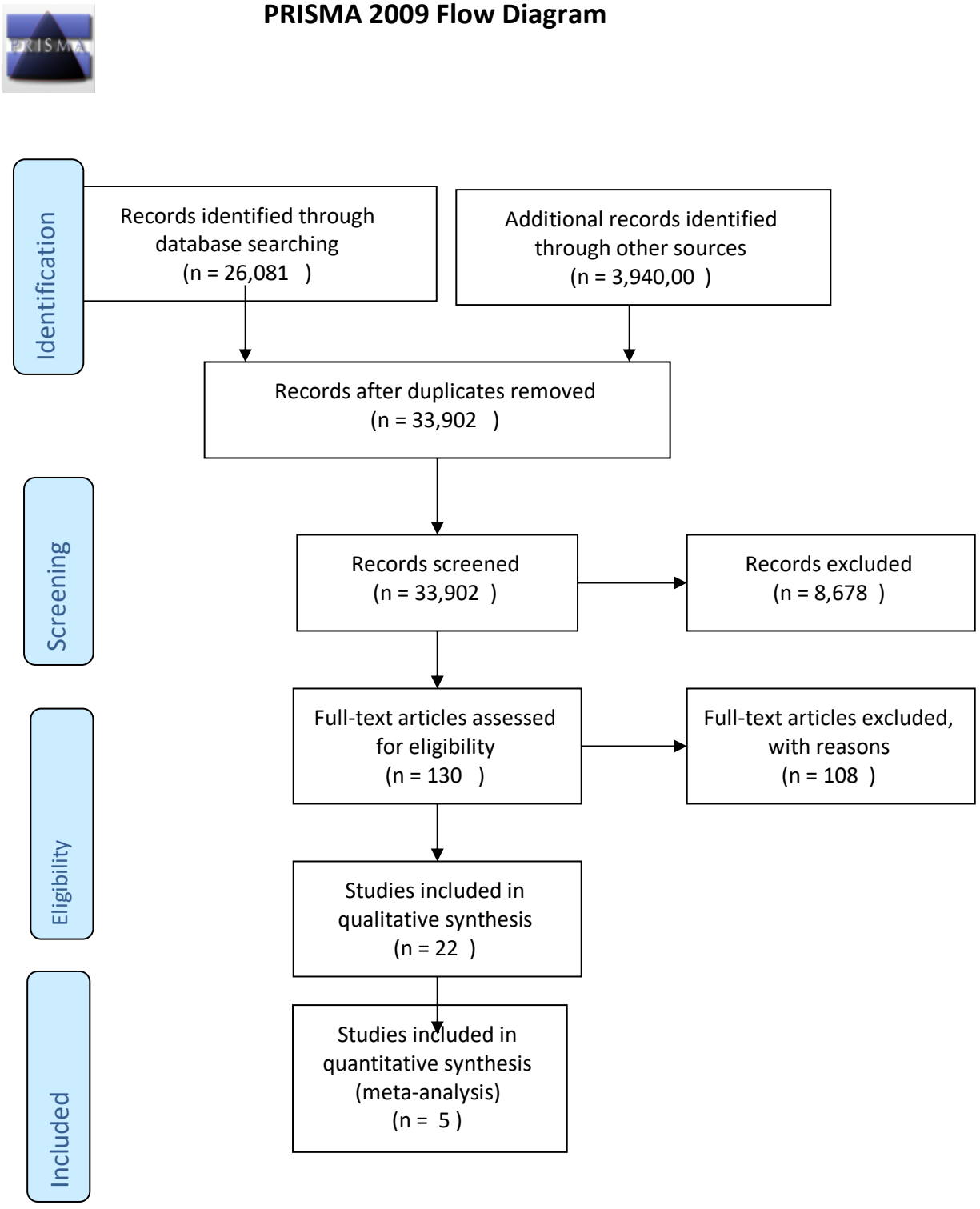

Figure 1. PRISMA Flow Diagram

A single-center randomized control trial by Morris et al. (2016) compared standardized rehabilitation therapy (SRT) to usual ICU care in patient's suffering with acute respiratory failure. The study began in 2009 and ended in 2014 with 300 total patients. Patients were randomly assigned using a computer-generated variably sized approach, 150 to SRT and 150 to control. Inclusion criteria consisted of patients who were admitted to a medical ICU, 18 years of age or older, receiving mechanical ventilation via endotracheal tube or noninvasive ventilation by mask, and had an arterial oxygen partial pressure to fraction inspired ratio less than 300. The intervention group received daily therapy interventions until discharge from the hospital. Interventions in the SRT group included passive range of motion, physical therapy, and progressive resistance exercise. Physical therapy consisted of bed mobility, transfer training, and balance training. Exercises included transferring to the edge of the bed, transferring to and from bed, and transferring to commode and chair. The control group received physical therapy during the weekday only when ordered by the physician. Among the 300 randomized patients, hospital length of stay did not decrease based on the implementation of standardized rehabilitation therapy. Secondary outcomes evaluated were the implications of CAM-ICU positive and CAM-ICU negative days to assess for the presence of delirium. Findings indicated there were no differences between groups as both groups had the same amount of CAM-ICU negative days (Appendix D).

Schweickert et al. (2009), in a two-university hospital study, assessed the efficacy of combining daily interruption of sedation with physical and occupational therapy on functional outcomes in patients receiving mechanical ventilation in the ICU. In this dual center study, 104 patients were randomly assigned using computer-generated permuted

block randomization. The 55 patients in the control group received daily interruption of sedation with therapy as ordered by the provider. Inclusion criteria included adults over the age of 18, those mechanically ventilated for less than 72-hours and expected to be intubated for more than 24 hours, and those who met baseline functional independence based on Barthel Index scoring of 70 or more points based on report by proxy for 2 weeks prior to admission. Assessment of the presence of delirium was identified utilizing the Richmond Agitation Sedation Scale (RASS) and Confusion Assessment Method for the ICU (CAM-ICU). Those 49 assigned to the intervention group received early exercise (physical therapy and occupational therapy) and mobilization with daily sedation interruption. Once deemed clinically stable, daily therapy was delivered and coordinated with daily sedation interruption until discharge or the patient returned to their previous level of function. Sessions progressed from active assisted to active independent range of motion in the supine position, to advancement to bed mobility activities, sitting balance activities, participation in activities of daily living, and exercises that encouraged increased independence with functional tasks. Eventual training included sit-to-stand, pre-gait exercises and walking. In regards to delirium, those in the intervention group were noted to have less ICU-delirium days then the control group, median of 2 days in the intervention group versus 4 days in the control. It was also noted as a secondary outcome that patients in the intervention group experienced less delirium in the ICU (33% to 57%, respectively, $p = 0.02$). Return to independent functional status at discharge occurred in 59% of patients in the intervention group, with 35% occurring in the control group. More ventilator free days were also noted in the intervention group

(23.5 days vs 21.1 days, respectively, $p = 0.05$) during the 28-day follow-up (Appendix E).

Schaller et al. (2016) in an international, multicenter, randomized controlled trial conducted at five university hospitals' surgical intensive care units hypothesized whether early mobilization leads to improved mobility, decreased length of stay, and increased functional independence at hospital discharge. A total of 200 patients were randomly assigned to either the intervention group or the control group. Randomization was performed using a randomized block design in a 1:1 ratio, stratified by Glasgow Coma Scale (GCS) greater than or less than 8 and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores through an access-restricted platform resulting in 104 assigned to the intervention group and 94 to the control group. Inclusion criteria included patients age 18 years or older, mechanically ventilated for less than 48 hours and expected to remain ventilated for a minimum of 24 hours at the time of screening, and were deemed to be functionally independent with a Barthel Index Score of 70 or more 2 weeks prior to admission based on proxy-collected information. Participants in both groups were managed by goal-directed sedation with daily awakening, daily spontaneous breathing trials, daily neurological assessment, and screenings for arousal, delirium, and pain intensity. The intervention group received the same level of clinical care as the control group as previously described with the addition of early, goal directed mobilization. The mobilization goal was defined daily on morning rounds and reflected the SICU Optimal Mobilization Score level: SOMS level 0 (bedrest); level 1 (passive range of motion in bed); level 2 (sitting); level 3 (standing); and level 4 (ambulation). Goal implementation was facilitated across shifts by inter-professional closed loop

communication. A multidisciplinary team approach was guided in each facility by a selected facilitator and included physicians, nurses, and physical therapists. Mobility in the control group was implemented using various individual SICU practice guidelines for mobilization and physical therapy. According to research, a lack of instruments to measure mobilization specifically in the SICU were noted, therefore the first step the researchers took was to create a numeric rating scale called the SICU optimal mobilization score (SOMS). This scale ranged from 0 (no mobilization) to 4 (ambulation) in order to help describe the patients' mobilization capacity during their SICU admission. Three main outcomes included the mean SOMS achieved during patients' stay in the SICU, patients' length of stay in SICU, and mini-modified functional independence measure score (mmFIM) at hospital discharge. Outcomes included improved mobilization in the intervention group based on SOMS score documented, decreased SICU length of stay (mean 7 versus 10 days, respectively, $p = 0.0054$), and improved functional mobility in the intervention group via the mmFIM score. Secondary and tertiary outcomes were also evaluated and discriminated between mobility-related and non-mobility related effects. For the mobility-unrelated outcomes, ICU delirium-free days were measured. ICU-delirium free days significantly differed between groups in the tertiary, mobility-unrelated subset in the patients of this study. Schaller et al. (2016) concluded that patients in the intervention group experienced less delirium days than the control group, with a $p = 0.0161$ (Appendix F).

Eggmann, Verra, Luder, Takala, & Jakob, (2018) conducted a randomized controlled trial that evaluated the effects of early progressive rehabilitation intervention in mechanically ventilated patients compared to standard early rehabilitation. This single

center international study was performed in a mixed ICU with mechanically ventilated adults whom were functionally independent prior to critical illness onset as reported by the family or referred from medical records. The control group received standard physiotherapy including early mobilization while the experimental group also received early mobility and physiotherapy with the addition of early endurance and resistance training. Primary outcomes were functional capacity (based on 6-Minute Walking Distance) and ability to perform activities of daily living (Functional Independence Measure [FIM]) at hospital discharge. There were no statistical differences between the control and experimental groups in regards to either the primary or secondary outcomes. Delirium was measured and recorded under ICU complications. It was noted that 64% of ICU days in the control group and 61% of the days in the experimental group were delirium free days ($p = 0.524$). At six-month follow up, quality of life post ICU admission was determined utilizing the Short Form 36 (SF-36), an instrument used to assess for long-term physical and mental health in ICU survivors. Although there were no significant differences between the patients whom completed the SF-36 and those who did not, a large amount of missing data was noted with only 36 out of 58 in the experimental group responding and 27 out of the 57 individuals in the control group (Appendix G).

A randomized control trial by Brummel et al. (2014) focused on the development of a cognitive therapy program for critically ill patients and assessed the feasibility and safety of administering combined cognitive and physical therapy during early critical illness. Participants included adults being treated for respiratory failure and/or septic, cardiogenic or hemorrhagic shock in the medical and surgical intensive care unit. Eighty-

seven patients were randomized to usual care, early one-daily physical therapy, or early one-daily therapy plus a progressive twice-daily cognitive therapy protocol. Cognitive therapy included orientation, memory, attention, problem solving activities, and other activities. Physical therapy was received by 17 out of the 22 usual care patients, 21 out of 22 of physical therapy only patients, and 42 out of 43 of cognitive plus physical therapy. Primary outcomes were feasibility data, cognitive, functional, and health-related quality of life outcome measures at three months. Secondary outcomes included days free of delirium, days free of mechanical ventilation, coma, ICU and hospital lengths of stay, mortality as well executive functioning, global cognitive status, and functional mobility at hospital discharge. Delirium was measured utilizing CAM-ICU. Results of the study suggested that combined interdisciplinary cognitive and physical therapy during early stages of critical illness is feasible and safe. There were no significant differences in secondary outcomes (Appendix H).

Critical Appraisal

CASP was utilized to critically appraise the five randomized controlled trials. In the study performed by Morris et al. (2016) the trial's aim was to compare standardized ICU rehabilitation to usual ICU care in acute respiratory failure. Utilizing the CASP, 'yes' was selected in all questions except three of them. In regards to blinding of participants, researchers were blinded to the randomization of assignment, but the patients and the personnel performing the rehabilitation were not blinded therefore received a "no" in this category. In regards to the question "if the groups were the same at the beginning of the trial", the answer selected was 'no' because although participants were admitted to an ICU, 18 years or older, with an arterial oxygen partial pressure ratio

less than 300, some patients received mechanical ventilation via endotracheal tube whereas others recived non-invasive mask ventilation. The other question response that was 'no' to was in regards to how large the treatment effect was and neither the primary or secondary outcomes of delirium were large enough to be statistically significant, although delirium was noted to occur less in the intervention group (Appendix I).

In the Schweickert et al. (2009) study, one question received the response "can't tell." It was difficult to decipher if patients, health workers, and study personnel were blinded to the treatment**.** Therapists who assessed patient's progress were not the same therapists as those who performed the intervention; however, therapists performing the intervention were aware of patient assignment to groups. Patients and families were instructed via a structured introductory statement not to discuss interventions performed but there is always a risk of accidental disclosure (Appendix J).

In the Schaller et al. (2016) study, responses were 'yes' to all questions answered in the appraisal. Improvement in mobility and delirium in their SICU population was statistically impacted and such a study could be applied to local practice. In this context, research was performed on functionally independent adults and did not include general SICU population, which could involve some constraints in application to general practice (Appendix K).

Eggmann et al. (2018) received a 'no' response in one out of eleven questions. The blinding of the patients, health workers, and study personnel did not occur throughout the study. The ICU staff were not blinded; however, physiotherapy assessors were blinded from which group patients were allocated and separate from the therapists providing the intervention. The primary care team made discharge decisions, which

would impact the length of involvement in the study, without input from the physiotherapists (Appendix L).

When appraising the Brummel et al. (2018) study, in four out of eleven questions the response was "yes" and three of the questions received a response of "can't tell." In regards to blinding, there were no comments on blinding of researchers or participants. The population included adults diagnosed with acute respiratory failure and those diagnosed with various forms of shock. Significant "no" answers involved the similarity of groups at the beginning of the study, how large was the treatment effect, and how precise was the estimate of the treatment effect. The treatment effect was not large enough to be statistically significant, and the study was not powered to allow determination of the efficacy of the interventions. Barriers to application to practice and population included having the resources required to provide trained professionals to adapt a type of cognitive therapy early in ICU patients to impede the development of cognitive impairment. However, the greater impact on delirium was noted in the early mobility group, which was determined to be feasible. Significant "no" answers involved the similarity of groups at the beginning of the study, how large was the treatment effect, and how precise was the estimate of the treatment effect. The treatment effect was not large enough to be statistically significant, and the study was not powered to allow determination of the efficacy of the interventions (Appendix M).

Cross Analysis

The randomized control trials were analyzed across studies to identify similarities and differences in the research findings. All studies included in this systematic review incorporated early mobility to patients who were critically ill and admitted to either an

ICU or a SICU. Population variances are noted within the selected studies. The population of the study conducted by Morris et al. (2016) included adult patients diagnosed with acute respiratory failure and included not only mechanically ventilated patients admitted to the ICU but also those whom required non-invasive ventilator support. Brummel at al. (2014) screened critically ill adult patients admitted to the ICU and SICU daily whom were being treated for respiratory failure, as well as cardiogenic, septic, or hemorrhagic shock. The population in their study also had distance limitations from the place of investigation, which disqualified patients from participating in the study. The remaining studies conducted by Schweickert et al. (2009), Schaller et al. (2016) and Eggmann et al. (2018) incorporated only mechanically ventilated patients in their studies.

The combination of interventions varied within each study implementing early mobilization against a variant. In the study conducted by Morris et al. (2016) patients in the usual care group (control) received weekday therapy when ordered by the clinical team while the intervention group received daily therapy until hospital discharge consisting of passive range of motion, physical therapy, and progressive resistance training in the study. Similarly, Schweickert et al. (2009) assigned patients to early exercise and mobilization during periods of daily interruption of sedation while the control group received therapy as ordered during sedation interruption. Schaller et al. (2016) utilized standard of care mobilization as their control, and as in the previously two mentioned studies, utilized early, goal-directed mobilization. Schaller et al. (2016) also included utilizing an interprofessional approach of closed-loop communication and the SICU optimal mobilization score (SOMS) algorithm. Eggmann et al. (2018) also utilized

early mobilization as part of their control group and assigned patients to the experimental group with early endurance and resistance training combined with mobilization. However, in the final study included by Brummel et al. (2014) individuals were randomly assigned to three separate care groups, one of which being early mobilization. The other variant interventions included usual care or early once-daily physical therapy plus novel, progressive, twice-daily cognitive therapy protocol.

As suspected, variance in the impact on delirium was noted among the studies. In the studies performed by Morris et al. (2016) and Brummel et al. (2014) there was no difference in delirium outcomes. Both studies utilized the CAM-ICU as the assessment instrument and reported a (p = 0.88) for CAM-ICU negative days (Morris et al. 2016) and delirium coma-free days (p=0.83) in the study performed by Brummel et al. (2014) with neither being statistically significant. In studies performed by Schweickert et al. (2009), median duration of ICU-associated delirium was decreased by nearly fifty percent in the intervention group that received early exercise and mobilization during periods of daily interruption of sedation than in the control group which was statistically significant (p = 0.02). Similarly, in the SICU population of Schaller et al. (2016), the intervention group was noted to be free from delirium for longer than control group, (p=0.016). In the study by Eggmann et al. (2018) delirium was decreased in the control group that received early-mobilization, while the intervention group that received early-mobilization with progressive resistance training were noted to have increased instances of delirium (p = 0.524).

Studies also independently measured delirium with validated assessment instruments. Morris et al. (2016), Schweickert et al. (2009) and Brummel et al. (2014)

utilized the CAM-ICU assessment tool to measure the presence of delirium in patients. Schaller et al. (2016) in their multi-center international study provided online supplemental documents, which outlined delirium measurements based on each research center's policy included in the study. Three out of the five centers included utilized CAM-ICU to assess for delirium. Two of the other study centers did not comment in their study protocol how delirium was assessed but mention assessment and importance of delirium. Eggmann et al. (2018) reported delirium-free days, which were assessed by a responsible physician without any pre-specified criteria, on ICU days, only at discretion of the physician.

Times at which delirium was assessed varied among the studies. Morris et al. (2016) measured delirium throughout the ICU stay. Similarly, Schweickert et al. (2009) assessed delirium daily until discharge from the hospital. Brummel et al. (2014) also assessed delirium, two times a day, until hospital discharge. Schaller et al. (2016) assessed for delirium until ICU discharge and Eggmann et al. (2018) assessed delirium on ICU days when assessed by a physician (Appendix N).

Next, the summary and conclusion section will be presented.

Summary and Conclusions

The purpose of this paper was to conduct a systematic review in order to determine if implementing the early mobility component of the ABCDEF bundle impacts delirium. Inclusion and exclusion criteria were developed by this author to guide this systematic review. Databases searched to obtain randomized controlled trials included Cinahl, PubMed, Google Scholar, and Medline. The PRIMSA checklist and flow diagram were used to guide the search. Five randomized control trials were selected based on the search strategy. After selection, articles were examined and pertinent information was gathered and entered into data collection tables were created by this author. Data included research design, purpose, setting, population, outcome variables, results, and limitations. A critical appraisal of each article was then performed guided by the CASP checklist. Lastly, a cross analysis was conducted in order to compare the similarities and differences in the findings.

Delirium continues to affect patients admitted to the critical care area. Delirium causes increased morbidity and mortality leading to chronic cognitive changes post discharge from the critical care areas. Early mobilization as part of the ABCDEF bundle has been found to improve delirium in patients admitted to the intensive care unit. Pun et al. (2019) concluded that the use of the complete bundle was associated with a decreased incidence of next-day mechanical ventilation, coma, delirium, physical restraint use, ICU readmission, and discharge to another facility other than home. According to Pun et al., there was a consistent dose-response relationship between implementation of the ABCDEF bundle and previously mentioned outcomes.

Early mobilization may be implemented safely among hemodynamically stable

critically-ill patients. Patients admitted to medical and surgical ICUs have been studied. Patients studied include those requiring invasive or non-invasive mechanical ventilator support as well as those suffering from various shock states.

In the five randomized control trials in this systematic review, improvement in delirium when implementing early mobility was noted. In the study performed by Schweickert et al. (2009), median duration of ICU-associated delirium was decreased by nearly half in the intervention group that received early exercise and mobilization during periods of daily interruption of sedation than in the control group ($p = 0.02$). Similarly, in the SICU population of Schaller et al. (2016), the intervention group was noted to be free from delirium for longer than control group (p=0.016).

Limitations to this systematic review were identified. The primary limitation was the comparison of early mobility to other forms of mobilization or physical therapy. Other limitations noted in the control trials were the various ages and population of patients included in the control trials. Lastly, the timing of delirium assessment and delirium assessment strategy was similar in some but not all of the studies. Early mobility was found to improve delirium in patients admitted to critical care, but more research needs to be conducted on early mobility as well as the ABCDEF bundle in regards to delirium and Post-Intensive Care Syndrome.

Despite limitations, this systematic review provides evidence that implementing the early mobility component of the ABCDEF bundle impacts delirium.

Next, recommendations and implications for advanced practice nursing will be discussed.

Recommendations and Implications for Advanced Nursing Practice

Prevention of the onset and duration of delirium is crucial to improving morbidity and mortality among critically ill patients. A culture of bedrest and immobility in the ICU has been found to not only impact duration of mechanical ventilation and the development of ICU-acquired weakness, but also onset and duration of delirium. Delirium has been shown to lead to chronic cognitive changes ranging from mild to severe. Early mobility, as part of the ABCDEF bundle, can aid the restoration of the physical, cognitive, and psychological dysfunction associated with critical care admissions. The nurse practitioner can act as a transformational leader to incorporate early mobility into the plan of care for hemodynamically stable patients admitted to the critical care areas.

Many methods have been highlighted in regards to decreasing the incidence and duration of delirium in critical care areas. Spontaneous breathing and awakening trials for mechanically ventilated patients, assessment and treatment of pain, as well as decreased use of benzodiazepines for sedation are examples of methods utilized for delirium management but one of the most recent interventions is early mobility in the hemodynamically stable patient. While certain criteria must be met, this non-pharmacological treatment has yielded improvement in delirium incidence and duration.

The most current literature was reviewed to provide evidence for this systematic review regarding early mobility. Evidence suggests that early mobility will improve the duration of delirium in critically ill patients, especially when combined with the interventions of the ABCDEF bundle. Educating nurse practitioners and healthcare providers is crucial to improving patient outcomes in critical care. With education and

evidence-based protocols, health care providers and the multidisciplinary team, including respiratory therapy and physical therapy, the intervention of mobility can be implemented on a clinical level. Although not a simple change in practice for institutions that do not utilize the ABCDEF bundle, adequate education and administrative support would aid in this transition for the critical care team.

This systematic review provides evidence that implementing the early mobility component of the ABCDEF bundle decreases the incidence and duration of delirium. Such improvement in delirium would improve patient morbidity and mortality after an admission to critical care. Most recent evidence as provided in this systematic review should guide the Advance Practice Registered Nurse and allow incorporating the ABCDEF bundle and current research evidence to the care of those in the critical care areas.

Further research must be conducted on delirium and early mobility to the as critically ill patients studied in this systematic review were of different ages and populations and early mobility was compared to various mobility interventions. Additional populations such as those whom are not deemed functionally independent at time of admission to the critical care areas should be further researched as most studies included in this systematic review focused on those whom were deemed functionally independent on admission. Randomized controlled trials utilizing the ABCDEF bundle and measuring delirium utilizing a pre-determined assessment instrument would assist in substantiating the bundle's effect on delirium.

Ethical and legal considerations must be taken into consideration when implementing any intervention to a population. The randomized controlled trials

included in this systematic review evaluated the risk to the patient populations without serious adverse events noted. Various level of cognitive impairment could render the patient unable to make an informed decision about such a change in the plan of care. Patient autonomy should be honored as exemplified by receiving informed consent from the patient or designee prior to any change in plan of care including implementation of early mobility and the ABCDEF bundle in the critical care areas. The multidisciplinary team must take into consideration the goals of care of the patient and their family and incorporate shared decision making to honor and respect the wishes of the patient (Hawryluck, Bouali, & Meth, 2011)

Diversity of patients should also be taken into consideration upon initiation of early mobility and the ABCDEF bundle. Providing appropriate resources and materials based on the educational level of the population would help foster better understanding and adherence to early mobility and the ABCDEF bundle. Exploring and explaining how the values and beliefs of the patient should be incorporated in the plan of care such as organizing early mobility around time for prayer or time spent with the family at the bedside. Cultural considerations such as language barriers should be evaluated, with appropriate teaching in the language preferred by the patient and the patient's designee.

Future recommendations include the use of early mobility among all patients admitted to the critical care areas. Studies have proposed that a dose-dependent effect of the frequency and complete use of the ABCDEF bundle, which includes early mobility, would improve patient outcomes in the critical care areas. It would also benefit future research if all aspects of PICS, including the psychologic, physical as well as cognitive were evaluated based upon administration of the ABCDEF bundle.

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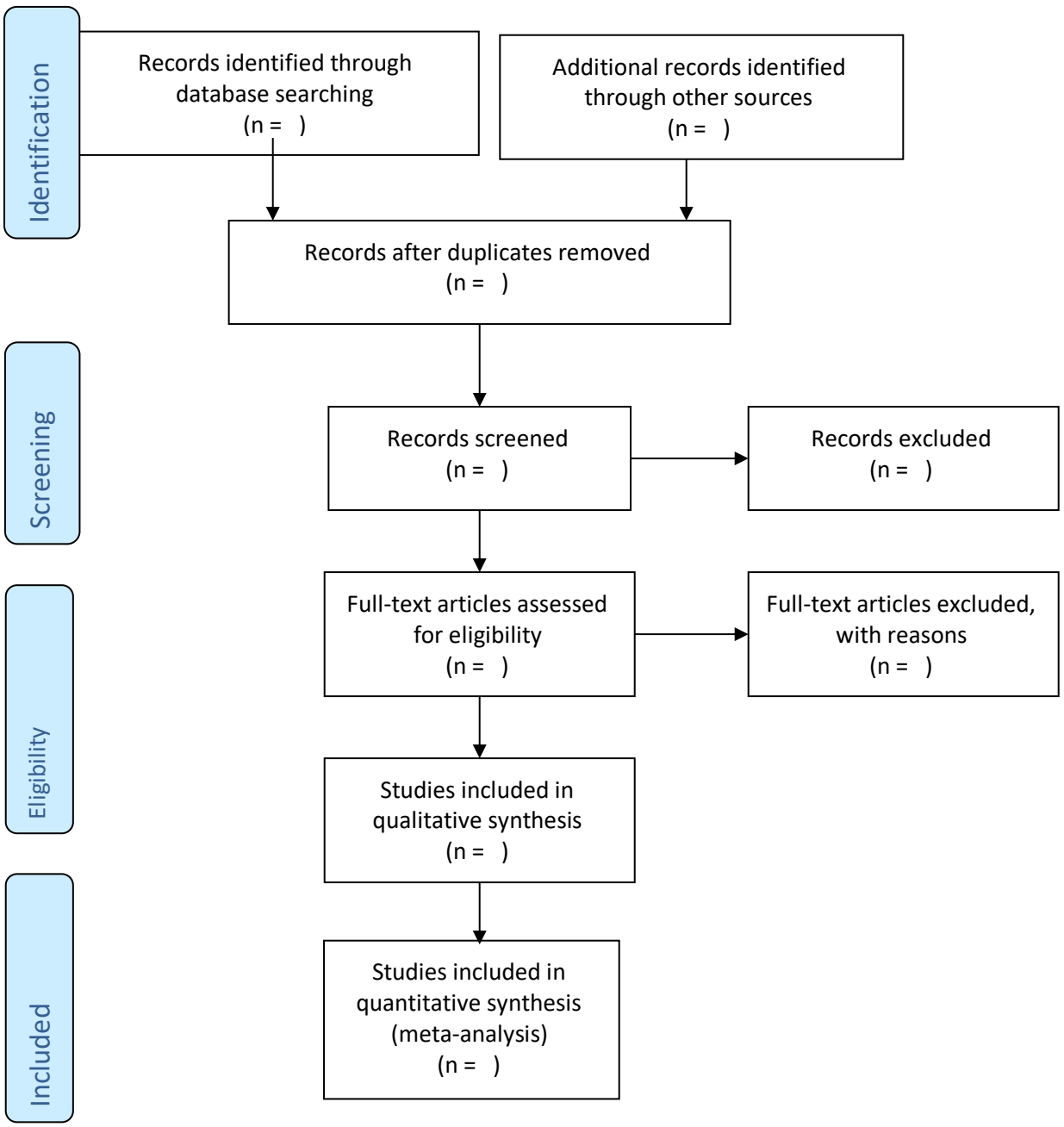
Appendix A

RASS	SAS
+4 Combative Combative, violent, immediate danger to staff	**7 Dangerous Agitation** Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, trashing side-to-side
+3 Very Agitated Pulls to remove tubes or catheters; aggressive	**6 Very Agitated** Requiring restraint and frequent verbal reminding of limits, biting ETT
+2 Agitated Frequent non-purposeful movement, fights ventilator	**6 Very Agitated** Requiring restraint and frequent verbal reminding of limits, biting ETT
+1 Restless Anxious, apprehensive, movements not aggressive	**5 Agitated** Anxious or physically agitated, calms to verbal instructions
0 Alert and Calm Spontaneously pays attention to caregiver	**4 Calm and Cooperative** Calm, easily arousable, follows commands
-1 Drowsy Not fully alert, but has sustained awakening to voice - eye opening and contact >10 seconds	**3 Sedated** Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
-2 Light Sedation Briefly awakens to voice - eyes open and contact <10 seconds	**3 Sedated** Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
-3 Moderate Sedation Movement or eye opening to voice - no eye contact	**3 Sedated** Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
-4 Deep Sedation No response to voice, but movement or eye opening to physical stimulation	**3 Sedated** Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again **2 Very Sedated** Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
-5 Unarousable No response to voice or physical stimulation	**1 Unarousable** Minimal or no response to noxious stimuli, does not communicate or follow commands

Retrieved from Marra et al., 2017, p. 19

Appendix B

PRISMA 2009 Flow Diagram



Appendix C

Critical Appraisal Skills Programme Instrument

	11 Questions	Yes	Can't tell	no
1	Did the trial address a clearly focused issue?			
2	Was the assignment of patients to treatments randomized?			
3	Were all the patients who entered the trial properly accounted for at its conclusion?			
4	Were patients, health workers and study personnel 'blind' to treatment?			
5	Were the groups similar at the start of the trial?			
6	Aside from the experimental intervention, were the groups treated equally?			
7	How large was the treatment effect?			
8	How precise was the estimate of the treatment effect?			
9	Can the results be applied in your context? (or to the local population?)			
10	Were all clinically important outcomes considered?			
11	Are the benefits worth the harms and costs?			

CASP (2019)

Appendix D

Morris, P.E., Berry, M.J., Files, C., Thompson, J.C., Hauser, J., Flores, L. … Young, M.P. (2016) Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure a randomized control trial. *JAMA* 315(24): 2694-2702. Doi:10.1001/jama.2016.7201

Table 1. Data Collection

Design	Purpose	Setting	Population
Single center randomized clinical trial	To compare standardized rehabilitation therapy to usual care in acute respiratory failure	Wake Forest Baptist Medical Center, North Carolina	Admission to ICU, being 18 years or older, mechanical ventilation via endotracheal tube or noninvasive ventilation by mask, arterial oxygen partial to fractional inspired oxygen ratio less than 300

Table 2. Data Collection

Outcome Variables	Results	Limitations
Hospital length of stay (LOS), ventilator days, ICU days, Intravenous sedation days, vasopressor days, ICU fluid balance, restraint days, CAM-ICU negative days, CAM-ICU positive days, RASS score of 4 or 5.	No difference in intervention vs control groups in number of vasopressor days, CAM-ICU positive or negative days, number of intravenous sedative days, restraint days, net ICU-related fluid balance, hospital LOS, ICU LOS, or RASS score.	Higher than expected drop out (lost to follow-up and withdrawals, 24%) post hospital discharge; no intervention following discharge; no explicit sedation protocol.

Appendix E

Schweickert, W.D., Pohlman, M.C., Pohlman, A.S., Nigos, C., Pawlik A.J., Esbrook C.L., … Kress, J.P. (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009; 373:1874–1882

Table 1. Data Collection

Design	Purpose	Setting	Population
Randomized control trial	Efficacy of combining daily interruption of sedation with physical and occupational therapy on functional outcomes in patients receiving mechanical ventilation in the ICU	Two ICUS located in two different university hospitals in the United States of America	Sedated adults (>18 years) on mechanical ventilation less than 72 hours with continuation of mechanical ventilation for 24 hours, met criteria for baseline functional independence prior to admission

Table 2. Data Collection

Outcome Variables	Results	Limitations
Number of patients return to independent functional capacity, number of hospital days with delirium, ventilator-free days during first 28-days of hospitalization, length of stay in ICU and hospital. At discharge: Barthel index score, number of functionally independent ADLs, distance walked without assistance, number of patients diagnosed with ICU-acquired paresis, hand-grip scoring at ICU and hospital discharge	Return to independent function at hospital discharge occurred in 59% of intervention group and 35% of control; patients in intervention group had higher Barthel index scores; intervention group had higher number of independent ADLs, intervention group had great unassisted walking distance, ICU-acquired paresis was noted at hospital discharge in 31% of intervention group, 49% in control. Hand grip	Knowledge of group allocation and witnessed interventions risk bias, neither center routinely performed physical and occupational therapy in patients receiving mechanical ventilation for less than 2 weeks without a developing neuromuscular disease. Select population- those who have functional independence prior to admission

	strength at hospital discharge did not differ. Median duration of ICU-associated delirium was half as long in patients in the intervention group, intervention group spent 23.5 days ventilator free, with control group 21.1, Length of stay in the ICU and hospital did not differ	

Appendix F

Schaller, S.J., Anstey, M., Blobner, M., Edrich, T. Grabitz, S.D., Gradwahl-Matis, I. … Eikermann, M. (2016) Early, goal-directed mobilization in the surgical intensive care unit: a randomised control trial. *Lancet* (88) 1377-1388.

Table 1. Data Collection

Design	Purpose	Setting	Population
Randomized control trial	To test whether early mobilization leads to improved mobility, decreased SICU length of stay, and increased functional independence at hospital discharge	Multicenter, international, parallel-group, assessor-blinded, randomized control trial in Surgical ICU (SICUs) of five university hospitals	Adults (>18 or older) mechanically ventilated for <48 hours, expected to be mechanically ventilated for greater than 24 hours whom were functionally independent (Barthel score of at least 70) 2 weeks prior to admission

Table 2. Data Collection

Outcome Variables	Results	Limitations
Primary outcomes mean SICU optimal mobilization score (SOMS), length of stay on SICU, and the modified functional independence mean score. Secondary outcomes (mobility related) daily serum glucose concentration, functional status at SICU discharge, length of stay in SICU before readiness for discharge, hospital length of stay, hospital mortality, 3-month mortality, discharge disposition.	Intervention group reached higher levels of mobilization earlier in SICU stay, had higher levels of mobilization at SICU discharge, 52% received SOMS level 4 (ambulating) versus 25% in control, SICU length of stay was decreased (p=0.0054), mobility realted functional independence scores were higher in intervention group than control (p=0.002), likelihood of complete functional	Bedside clinicians were not masked to group assignment. Generalizability to non-surgical ICU patients or non-ventilated surgical ICU patients may be restricted due to population, patients had no functional limitation prior to admission, low volume of ventilated patients in SICU, patients transitioned to comfort care during study, protocols for control group varied between study

Secondary outcomes (non-mobility related): ICU delirium-free days, ventilator-free days, mean daily morphine equivalent dose (mg), numbers of days receiving corticosteroids, daily high serum sodium concentration.	independence was higher in intervention than control (p=0.0030), mmFIM was improved in intervention at hospital discharge. For mobility-unrelated outcomes, only significant outcomes included ICU-delirium-free days, with intervention group free from delirium for longer than control group (p=0.0161)	centers. High proportion lost to follow-up.

Appendix G

Eggmann, S., Verra, M.L., Luder, G., Takala, J., Jakob, S.M. (2018) Effects of early, combined endurance training in mechanically ventilated, critically ill patients: A randomised control trial. PLoS ONE 13(11): 1-19 doi: 10.1671.journal.pone.0207428

Table 1. Data Collection

Design	Purpose	Setting	Population
Randomized control trial	Evaluate effects of early progressive rehabilitation intervention in mechanically ventilated patients compared to standard early rehabilitation.	Tertiary mixed ICU of the Department of Intensive Care Medicine at the Inselspital, Bern University Hospital, Switzerland	Adults over the age of 18, expectation of duration of mechanically ventilation for 72 hours or more, independent prior to onset of critical illness determined by patient's chart and family report

Table 2. Data Collection

Outcome Variables	Results	Limitations
Primary outcomes were functional capacity (based on 6-Minute Walking Distance) and ability to perform activities of daily living (Functional Independence Measure [FIM]) at hospital discharge. Secondary outcomes included FIM at ICU discharge and muscle strength at ICU discharge. Further outcomes included time requiring mechanically ventilation, time spent in ICU, hospital length of stay, ICU mortality, hospital mortality, ICU	Primary outcomes were significant for improved 6-minute walking distance p = 0.542 in the intervention group. No significant difference between intervention or control at ICU and hospital discharge. In regards to ICU complications, Delirium free ICU days were higher in the control group, with a p = 0.524	Blinding of participants and physiotherapists was not obtained. Hetergenous population. Difficulty in group separation and exercise dose. Loss of follow up and unequal between group (41% versus 58%). Targeted population, limits applicability to those without functional independence prior to critical illness. SF-36 was not adequately powered, Type-I error, could affect interpretation of results.

complications including delirium-free days, as well as quality of life 6 months after discharge utilizing Short Form 36. Physiotherapy, ICU treatment, and ICU medication use was also detailed and compared amongst the control and experimental group.		

Appendix H

Brummel, N.E., Girard, T.D., Ely, E.W., Panharipande, P.P., Morandi, A., Hughes, C.G. … Jackson, J.C. (2014) Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the activity and cognitive therapy in ICU (ACT-ICU) trial. *Intensive Care Med.* 40(3): 370-379. Doi:10.1007/s00134-013-3136-0

Table 1. Data Collection

Design	Purpose	Setting	Population
Randomized control trial	Development of a cognitive therapy program for critically ill patients and assessed the feasibility and safety of administering combined cognitive and physical therapy during early critical illness.	Medical Intensive Care Unit and Surgical Intensive Care Unit at the Vanderbilt University Medical Center, Nashville, TN	Adults over the age of 18, being treated for respiratory failure and/or septic, cardiogenic or hemorrhagic shock who resided within 120 miles of Nashville TN

Table 2. Data Collection

Outcome Variables	Results	Limitations
Primary outcomes were feasibility data, cognitive, functional, and health-related quality of life outcome measures at three months. Secondary clinical outcomes included days free of delirium, coma, days free of mechanical ventilation, ICU and hospital lengths of stat and	Primary outcomes: combined interdisciplinary cognitive and physical therapy during early stages of critical illness is feasible and safe Secondary outcomes: follow-up outcomes, measure of executive functioning, global cognition, functional mobility, ADL status IADL	Small sample size, single center enrollment, inability to blind patients or those performing the intervention which may introduce bias, inability to provide cognitive therapy while patients were in rehabilitation facilities or nursing homes

mortality. Executive functioning, global cognitive status, and functional mobility at hospital discharge.	status, quality of life status, delirium free, come free days, ventilator free days, ICU and hospital length of stay, mortality and cognitive or functional outcomes at hospital discharge did not differ between groups.	

Appendix I

Morris, P.E., Berry, M.J., Files, C., Thompson, J.C., Hauser, J., Flores, L. … Young, M.P. (2016) Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized control trial. *JAMA* 315(24): 2694-2702. Doi:10.1001/jama.2016.7201

	11 Questions	**Yes**	**Cant' tell**	**No**
1	**Did the trial address a clearly focused issue?** The trial's aim was to compare standardized rehabilitation treatment (SRT) to usual ICU care in acute respiratory failure with the objective of improving patient outcomes.	✖		
2	**Was the assignment of patient to treatments randomized?** Both groups were assigned randomly using a computer generated variably size approach.	✖		
3	**Were all the patients who entered the trial properly accounted for at the conclusion?** Out of the 300 patients randomized, 150 were assigned to SRT and 150 to control. Of the SRT group, 18 died, 1 withdrew. Out of the 131 discharged, 15 died before 6 month follow up, 3 withdrew, and 29 were "lost to follow up" with only 84 completing 6-month follow-up. Out of 150 assigned to the control group, 18 died and 6 withdrew prior to hospital discharge, out of the 126 discharged from the hospital, 15 died, 5 withdrew, and 25 were "lost to follow up" leaving 81 who completed 6 month follow-up.	✖		
4	**Were patients, health workers, and study personnel 'blind' to treatment?** Researchers, as well as follow-up research personnel were blinded to randomization assignment. Personnel performing rehabilitation and patients were not blinded to physical therapy being performed.			✖
5	**Were the groups similar at the start of the trial?** All patients were admitted to the medical ICU, 18 years or older, with an arterial oxygen partial pressure ratio less than 300. However, some patients received mechanical ventilation via endotracheal tube or non-invasive mask ventilation.			✖
6	**Aside from the experimental intervention, were the groups treated equally?** Inclusion and exclusion criteria were stratified prior to rehabilitation. The amount of exercise delivered was substantially different between SRT and control. The SRT received significantly more passive range of motion, physical therapy, and progressive resistance exercise, 87%, 55%, and 36% respectively. The control group only received physical therapy 12% of study days.	✖		

7	**How large was the treatment effect?** The median hospital LOS for intervention group was 10 days, 10 days for the usual care group, P 0.41. CAM-ICU negative days P 0.88, CAM-ICU positive days 0.77. Neither were statistically significant.			✖
8	**How precise was the estimate of the treatment effect?** P <0.05 for each outcome and testing was 2-sided. Secondary outcomes, due to lack of adjustment for multiple testing, should be considered exploratory.	✖		
9	**Can the results be applied in your context? (or to the local population?)** Early mobilization in the SRT group did not result in patient harm or increase prevalence of adverse events, would be safe and appropriate to perform based on these results.	✖		
10	**Were all clinically important outcomes considered**? The primary outcome of hospital length of stay was assessed as well as other outcomes including secondary outcomes including ventilator days, vasopressor days, and delirium were assessed.	✖		
11	**Are the benefits worth the harms and costs?** No difference was noted in adverse events reporting between study groups.	✖		

Appendix J

Schweickert, W.D., Pohlman, M.C., Pohlman, A.S., Nigos, C., Pawlik A.J., Esbrook C.L., … Kress, J.P. (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: A randomised controlled trial. Lancet. 2009; 373:1874–1882

	11 Questions	Yes	Cant' tell	No
1	**Did the trial address a clearly focused issue?** Assessed the efficacy of combining daily sedation interruption with physical and occupational therapy on functional outcomes, which constituted returning to independent functional baseline at hospital discharge due to prevalence of ICU-acquired weakness and neuropsychiatric disease secondary to immobility.	✖		
2	**Was the assignment of patient to treatments randomized?** Patients were randomly assigned by computer-generated, permuted block randomization to the early mobilization and exercise group during periods of daily sedation interruption (intervention) or to daily sedation with therapy as ordered by the primary care team.	✖		
3	**Were all the patients who entered the trial properly accounted for at the conclusion?** Total 104 patients randomized, 49 assigned to intervention and 55 patients assigned to control. None were discontinued from protocol, none were lost to follow up. Nine patients died in the intervention group, 14 patients died in the control group all before hospital discharge.	✖		
4	**Were patients, health workers, and study personnel 'blind' to treatment?** Group of assessment therapists were distinct from the therapists who performed the intervention. The therapists performing the intervention were aware of patient selection to intervention or control group. The patients and family were instructed via a structured introductory statement, not to discuss interventions performed. Assessments by blinded therapists were performed in the afternoon, after morning physical therapy.		✖	
5	**Were the groups similar at the start of the trial?** All patients were adults, been on mechanical ventilation less than 72 hours, expected to continue mechanical ventilation greater than 24 hours, and had met criteria for baseline functional independence (Barthel Index >70) from a proxy describing patient function 2 weeks prior to admission.	✖		

6	**Aside from the experimental intervention, were the groups treated equally?** No differences noted in frequency of daily mobility, assessment of hemodynamic stability, or progression of care (i.e. extubation). Intervention(s) were stopped once either patient returned to prior independent functional status or discharged.	✖		
7	**How large was the treatment effect?** Return to independent functional status at discharge; 59% in intervention group and 35% in patients in the control group ($p = 0.02$) Patients were noted in the intervention group to have shorter duration in delirium ($p=0.02$) and more ventilator free days ($p = 0.05$) during 28 day follow-up.	✖		
8	**How precise was the estimate of the treatment effect?** Calculated that a total sample size of 100 patients would be needed to detect a 30% difference in the number of patients achieving return to independent functional status between two groups with 80% power and a two-sided significance of 0.05.	✖		
9	**Can the results be applied in your context? (or to the local population?)** Implications of utilizing a structured physical rehabilitation program led to statistically significant outcomes in patients with baseline functional independence. However, lacks ability to generalize results to patients where preadmission functional capacity is limited.	✖		
10	**Were all clinically important outcomes considered?** Functional status at discharge, discharge disposition, as well as other secondary outcomes were reviewed including patient specific diagnosis and correlation with clinical outcomes.	✖		
11	**Are the benefits worth the harms and costs?** Serious adverse events were uncommon, in 498 physical therapy and occupational therapy sessions, one instance of desaturation less than 80%, one radial arterial line was inadvertently removed, no accidental extubation documented. Most common patient instability noted was perceived ventilator asynchrony.	✖		

Appendix K

Schaller, S.J., Anstey, M., Blobner, M., Edrich, T. Grabitz, S.D., Gradwahl-Matis, I. … Eikermann, M. (2016) Early, goal-directed mobilization in the surgical intensive care unit: A randomized control trial. *Lancet* (88) 1377-1388.

	11 Questions	**Yes**	**Cant' tell**	**No**
1	**Did the trial address a clearly focused issue?** Investigated whether early mobilization in critically ill patients admitted to a surgical intensive care unit (SICU) would improve mobility, decrease SICU length of stay, and increase independence of patients at hospital discharge.	✖		
2	**Was the assignment of patient to treatments randomized?** Patients were randomly assigned utilizing a stratified block randomization via a restricted web platform.	✖		
3	**Were all the patients who entered the trial properly accounted for at the conclusion?** Out of the 104 randomly assigned to the intervention, 7 were excluded during hospitalization leading to an intervention group of 97. 57 were then lost to 3 month follow up, leaving 40 individuals that fully completed the three month follow up survey. Out of the 96 assigned to the control, none were excluded during the hospitalization. However, at 3 month follow up, only 44 individuals completely answered the survey.	✖		
4	**Were patients, health workers, and study personnel 'blind' to treatment?** Patients in the intervention group received the same level of clinical care as the control group except for early, goal-directed mobilization.	✖		
5	**Were the groups similar at the start of the trial?** All patients were admitted to SICU, adults, were mechanically ventilated for less than 48 hours, expected to require mechanically ventilation for greater than 24 hours, were functionally independent at baseline based on Barthel Index Score of 70 or more 2 weeks before admission, based on patient or proxy report. However, the surgeries performed on the patient's varied.	✖		
6	**Aside from the experimental intervention, were the groups treated equally?** All patients received goal-directed sedation with daily awakening trials, daly neurologic assessments, screening for arousal, delirium, and pain intensity, and regular evaluation for early enteral feeding.	✖		
7	**How large was the treatment effect?** Higher levels of mobilization earlier in SICU stay, had higher levels of mobilization at SICU discharge, 52% received SOMS level 4 (ambulating) in the intervention	✖		

	group versus 25% in control, SICU length of stay was also decreased (p=0.0054). For mobility-unrelated outcomes, only significant outcomes included ICU-delirium-free days, with intervention group free from delirium for longer than control group (p=0.0161).			
8	**How precise was the estimate of the treatment effect?** Estimated that enrolling 100 patients in each treatment group, based on previous studies the researchers investigated, would result in great than 80% power to identify an inter-group difference with a two-sided α error of 0.05. If p level was the predefined α error the procedure was terminated.	✖		
9	**Can the results be applied in your context? (or to the local population?)** Improvement in mobility and delirium in the SICU population cared for was impacted and could be applied to practice. However, research was only performed on functionally independent adults and did not reflect impact on the general SICU population.	✖		
10	**Were all clinically important outcomes considered?** Mobility related and mobility unrelated outcomes were addressed.	✖		
11	**Are the benefits worth the harms and costs?** 35 adverse events in 2164 ICU days related to mobilization, ten cases in the control and twenty-five in the intervention. Hypotension was reported mostly, then categorized minor events such as dyspnea, dizziness, tachypnea, or sinus tachycardia, desaturation to less than 90% and a single instance of dislodgment of an arterial line as well as nasogastric tube. No events with death resulting or increase in hospital mortality were noted in the study.	✖		

Appendix L

Eggmann, S., Verra, M.L., Luder, G., Takala, J., Jakob, S.M. (2018) Effects of early, combined endurance training in mechanically ventilated, critically ill patients: A randomized control trial. PLoS ONE 13(11): 1-19 doi: 10.1671.journal.pone.0207428

	11 Questions	**Yes**	**Cant' tell**	**No**
1	**Did the trial address a clearly focused issue?** The goal was to evaluate the impact of early, combined endurance training in mechanically ventilated patients with early mobility on functional impairment in critical care survivors.	✖		
2	**Was the assignment of patient to treatments randomized?** Unrestricted computer generated randomization was performed by a study nurse partly involved in screening eligible candidates.	✖		
3	**Were all the patients who entered the trial properly accounted for at the conclusion?** 56 were assigned to the experimental group, 1 died before the intervention, 49 were able to complete the FIM assessment, a total of 10 died prior to discharge and 4 were either transferred to another facility or unexpectedly discharged with only 44 completing the 6-minute walk test. Only 34 of the intervention group completed the SF-36 assessment. 57 were part of the control group, 56 received the intervention in critical care, one was transferred to another facility and three were unexpectedly discharged. Only 46 completed the FIM assessment, a total of 14 died during the hospitalization, 39 completed the 6 minute walk test assessment and only 24 completed the 6 month follow up SF-36 assessment.	✖		
4	**Were patients, health workers, and study personnel 'blind' to treatment?** ICU staff were not blinded, physiotherapy assessors were blinded from group allocation and separate from the therapists providing the intervention. However, therapist separation was not prevented between the two groups. Discharge decisions were made by the primary care team without input from the physiotherapists.			✖
5	**Were the groups similar at the start of the trial?** All were adults, admitted to the ICU, who were intubated for at least 72 hours and had been independent before the onset of critical illness.	✖		
6	**Aside from the experimental intervention, were the groups treated equally?** Both groups received standard ICU care with protocol-guided sedation, weaning, and nutrition. In case of re-admission, the patients were	✖		

	reassigned to the treatment allocation for either intervention or control based on clinical status.			
7	**How large was the treatment effect?** No statistical significance between primary outcomes of 6-minute walk test (p=0.542) or functional independence (p=0.308). Secondary outcomes, including delirium free ICU days were 64% in the early mobility group and 61% in combined endurance and resistance training group, p = 0.524, not statistically significant.	✖		
8	**How precise was the estimate of the treatment effect?** A statistical power of 80% and an α level of 0.05 required a sample size of 72 patients, further adjusted by 28 patients due to two primary outcomes that were expected to highly correlate, but lastly increased 15% to 115 participants due to high attrition such as mortality.	✖		
9	**Can the results be applied in your context? (or to the local population?)** In this case, there was little clinical benefit to adding endurance and resistance training as the control group of early mobility produced nearly the same results. There were also more delirium free days in the control group than the intervention group.	✖		
10	**Were all clinically important outcomes considered?** Appropriate mobility outcomes, as well as secondary mobility outcomes including delirium, sedation, ventilator days, were evaluated.	✖		
11	**Are the benefits worth the harms and costs?** Adverse events were rare and without serious injury to the patient per the study	✖		

Appendix M

Brummel, N.E., Girard, T.D., Ely, E.W., Panharipande, P.P., Morandi, A., Hughes, C.G. … Jackson, J.C. (2014) Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: The activity and cognitive therapy in ICU (ACT-ICU) trial. *Intensive Care Med.* 40(3): 370-379. doi:10.1007/s00134-013-3136-0

	11 Questions	**Yes**	**Cant' tell**	**No**
1	**Did the trial address a clearly focused issue?** To assess the feasibility and safety of administering combined cognitive and physical therapy early during a critical illness and it's impact on cognitive impairment.	✖		
2	**Was the assignment of patient to treatments randomized?** A computer generated permuted-block randomization was used to assign the patients to one of the three groups.	✖		
3	**Were all the patients who entered the trial properly accounted for at the conclusion?** 22 were assigned to usual ICU care (control) 6 died in the hospital, 3 died after discharge, and 13 were alive at 3 months after discharge, only 12 were assessed with one being unavailable. 22 were assigned to the early mobility physical therapy group, 6 died during the hospitalization, 1 died after discharge, 15 were alive 3 months after discharge and only 14 were assessed. 43 were assigned to the cognitive and physical therapy group, 11 died in the hospital, 4 withdrew in the hospital, 32 were discharged alive, 5 died after discharge and out of the 27 alive at 3 month follow up only 18 were assessed with two being unavailable.	✖		
4	**Were patients, health workers, and study personnel 'blind' to treatment?** No comment on how blinding or if it did occur.		✖	
5	**Were the groups similar at the start of the trial?** Various diagnosis of either respiratory failure and or septic, cardiogenic or hemorrhagic shock whom were critically ill less than 72 hours and lived within 120 miles of Nashville, TN.			✖
6	**Aside from the experimental intervention, were the groups treated equally?** All patients received standard ICU/SICU care.	✖		
7	**How large was the treatment effect?** No statistical difference noted in either primary or secondary outcomes.			✖

8	**How precise was the estimate of the treatment effect?** The study was not powered to allow determination of the efficacy of the interventions.			✖
9	**Can the results be applied in your context? (or to the local population?)** It is feasible to adapt a type of cognitive therapy early in ICU patients to impede the development of cognitive impairment. This would require the appropriate resources and trained professionals but more research would need to be conducted regarding this intervention.		✖	
10	**Were all clinically important outcomes considered?** Would have been beneficial to evaluate mechanically ventilation specific outcomes such as ventilator days, sedation use, etc. Would have been interesting to monitor mobility effects as well as non-mobility related outcomes.			✖
11	**Are the benefits worth the harms and costs?** There was a noted adverse event of acute back pain with resulting hypertension, but no account of patient harm was noted**.**	✖		

Appendix N

Cross Analysis

Author	Early Mobility	Effect on Delirium	Measure of Delirium	Time Measured (days, weeks, months, years)
Morris, et al. (2016)	Mechanically ventilated patients in the control (usual care) group received weekday therapy when ordered by the clinical team. The intervention group received daily therapy until hospital discharge consisting of passive range of motion, physical therapy, and progressive resistance training.	No differences in intervention vs control in CAM-ICU positive p = 0.77 or CAM_ICU negative days p=0.88.	CAM-ICU, delirium free days. No disclosure on how often CAM-ICU assessment performed per day per patient.	Total, upon ICU discharge
Schweickert, et al. (2009)	Mechanically ventilated patients randomly assigned to intervention group or control group. Intervention group received early exercise and mobilization during periods of daily interruption of sedation; control group received therapy as ordered during sedation interruption.	Median duration of ICU-associated delirium was nearly half as long (33%) in patients in the intervention group than in the control group (55%), p = 0.02.	CAM-ICU, daily	Daily, until discharge from hospital. Summarized in results under ICU delirium days and hospital delirium days.
Schaller, et al. (2016)	Mechanically ventilated patients were randomly assigned to the	ICU-delirium-free days, with intervention group free from	Referred to supplemental material from authors:	Until ICU discharge

	control group of standard of care mobilization, or early, goal-directed mobilization utilizing an interprofressional approach of closed-loop communication and the SICU optimal mobilization score (SOMS) algorithm.	delirium for longer than control group (p=0.0161)	Massachusetts General Hospital, Boston, MA – CAM-ICU two times a day Universitatit Munchen, Munich, Germany – CAM-ICU every 8 hours Paracelsus Medical University Salzburg, Austria – not specified Beth Israel Deaconess Medical Center – not specified UMASS Medical Center, Worcester, MA – CAM-ICU, not specified frequency	
Eggmann, et al. (2018)	Mechanically ventilated patients were randomly assigned to standard physiotherapy including early mobilization or to the experimental group with early endurance and	Delirium free ICU days were higher in the control group (early mobility group 64%), with experimental group being delirium free	Assessed by responsible physician with any pre-specified criteria, on ICU days only at discretion of the physician	ICU days, by discretion of physician

	resistance training combined with mobilization	61% with a p = 0.524		
Brummel, et al. (2014)	Patients were randomly assigned to three groups: usual care, early-once daily physical therapy, or early once-daily physical therapy plus novel, progressive, twice-daily cognitive therapy protocol	Delirium-free days did not differ between the three groups at hospital discharge.	CAM-ICU, two times a day	Twice daily, until hospital discharge.