Vanderbilt ICU Recovery Program (VIP): A Quality Improvement Pilot

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Study Schema

1.0 Summary

Title: Vanderbilt ICU Recovery Program (VIP): A Quality Improvement Pilot

Background: Every year, millions of Americans are admitted to the intensive care unit. Due to advances in critical care, mortality rates are decreasing, increasing the number of ICU survivors. Survivors of critical illness, however, often face physical, functional, and cognitive deficits that place them at risk for a cycle of re-hospitalization that frequently culminates in premature death. Moreover, post-ICU interventions may be resource-intensive and may be most cost-effective only in a subgroup of patients at highest risk. Whether a multi-disciplinary program to facilitate recovery from critical illness can prevent hospital readmission and improve quality of life among high-risk ICU survivors remains unknown.

Primary Aim:

- To examine the feasibility of implementing a multidisciplinary ICU Recovery Program and the influence of such a program on process measures including contact with the ICU recovery team and attendance of ICU recovery clinic.

Secondary Aims:

- To compare the effect of an ICU Recovery Program on 30-day same-hospital readmission experienced by ICU survivors at high risk of readmission.
- To compare the effect of an ICU Recovery Program on the hospital length of stay and 30-day mortality experienced by ICU survivors at high risk of readmission.

Primary Hypothesis:

- Implementation of a multidisciplinary ICU Recovery Program will be feasible and will increase contact with the ICU Recovery Team and attendance of the ICU Recovery Clinic.

Secondary Hypotheses:

- A multi-disciplinary ICU Recovery Program will decrease the incidence of 30-day same-hospital readmission experienced by ICU survivors.
- A multi-disciplinary ICU Recovery Program will not affect the hospital length of stay or 30-day mortality experienced by ICU survivors at high risk of readmission.

Inclusion Criteria:

1. Age ≥ 18 years
2. Admitted to the Medical Intensive Care Unit (MICU) at Vanderbilt University Medical Center for at least 48 hours
3. Estimated risk of 30-day same-hospital readmission greater than 15%

4. Not previously enrolled in the study.

Exclusion Criteria:

1. Long-term residence at a skilled nursing facility
2. Long-term mechanical ventilation prior to admission
3. Solid organ or stem cell transplantation
4. Recorded primary residency > 200 miles from Vanderbilt
5. Comfort care only

Consent: Because both usual care and the addition of a multi-disciplinary ICU Recovery Program are within the current standard of care and there are no known risks or benefits to either approach, the study is felt to present minimal risk. As study group assignment would occur immediately at or prior to ICU admission and nearly all ICU patients might conceivably be eligible, obtaining individual informed consent is felt to be impracticable. Given the minimal risk and impracticability of consent, we will seek waiver of informed consent when examining the feasibility of implementing this ICU Recovery Program into practice.

Randomization: Vanderbilt's Office of Quality, Patient Safety and Risk Prevention displays an estimated risk of 30-day same-hospital readmission for a random half of patients admitted to Vanderbilt University Medical Center. The risk score and group assignment generated at hospital admission by the Cornelius Quality Improvement Project will be used for the current study.

Study Interventions:

- **Usual Care:** Patients will receive post-ICU care as dictated by their clinical team.
- **ICU Recovery Program:** Patients will receive a 10-component ICU Recovery Program intervention including: (1) a nurse practitioner in-person visit between ICU transfer and hospital discharge, (2) an ICU Recovery Program pamphlet, (3) a pharmacist medication reconciliation at the time of ICU transfer, (4) an ICU Recovery Program contact line, (5) a nurse practitioner history and physical in ICU Recovery Clinic, (6) a pharmacist medication reconciliation in ICU Recovery Clinic, (7) a cognitive/mental health assessment and psychoeducation in ICU Recovery Clinic, (8) a case management consultation in ICU Recovery Clinic, (9) a patient centered consultation with PCCM physician in ICU Recovery clinic, (10), directed subspecialty referrals.

Endpoints:

- **Primary:** Number of ICU Recovery Program intervention components received.
- **Secondary:** 30-day same-hospital readmission, hospital length of stay, mortality

2.0 Background

Accelerating ICU Admissions and Decreasing Mortality: The Problem of Survivorship.

Every year, more than 6 million people in North America are admitted to a general medical or general surgical intensive care unit (ICU). Hospitalizations for the most common life-threatening critical illnesses such as sepsis and Acute Respiratory Distress Syndrome (ARDS) are significantly increasing(1). Due to advances in critical care, mortality rates have significantly declined for many critical illness diagnoses, bolstering the ranks of ICU survivors. However, the cost of survivorship is high. These individuals are alive yet suffer from new and persistent deficits(2). Their post-critical illness challenges are challenges of survivorship, marked by burdens and legacies of critical illness, including physical, functional, mental health, and cognitive deficits and a cycle of re-hospitalizations, frequently culminating in premature death(3–6).

Mortality and Rehospitalization in Survivors of Critical Illness.

Survivors of critical illness have a high risk of death and hospital readmission in the first month after ICU discharge(7, 8). In a recent analysis of pilot data in 447 ICU survivors at Vanderbilt University Medical Center, 40% of individuals had been hospitalized at least once between discharge and 3 months and approximately half had been re-hospitalized at least once in the year following hospital discharge. Similar findings have been reported elsewhere, with a recent investigation in the *American Journal of Medical Science* reporting that half of ICU survivors are re-admitted to the hospital or the ICU in the 12 months after discharge(9). Although much attention has been given to elderly and previously ill patients cared for in ICUs, one recent study found that excess mortality and hospital costs after critical illness were highest in younger patients without significant comorbidity(10). Importantly, 40% of readmissions within 90 days of a hospitalization for sepsis were found to be potentially avoidable(11).

Tailored Treatment to Improve Outcomes in Survivors Critical Illness – A Conspicuous "Gap."

Multidisciplinary programs designed for cohorts such as heart failure patients and cancer survivors are rapidly proliferating(12), yet programs tailored to care for survivors of critical illness are extremely rare. Interest in the topic of "ICU survivors" has grown explosively since 1990, as reflected in a ~ 3,000 % increase in in PubMed indexed citations in the last 25 years. Yet, few institutions have developed and implemented ICU Recovery Programs, and whether such programs can be effectively delivered to patients remains unknown.

Survivorship Care: A Survey of Early Attempts to Improve Outcomes in ICU Survivors.

Interdisciplinary programs designed for survivors of other medical conditions – largely cancer – have multiplied since the early 2000s(12). Over 300 cancer survivorship

programs exist. The services they provide are increasingly viewed as indispensable to excellent cancer care (many clinicians would characterize them as "standard of care"; evidence from numerous studies has shown that they improve a wide range of patient centered outcomes(13). In contrast, though ICU Recovery Programs are of interest at many centers across the United States, there is currently very little experience with their development and implementation, and no data to suggest whether they may improve patient-centered outcomes.

The small number of studies available about ICU Recovery Programs have been done outside the U.S. and have not shown clear benefit. A British trial investigating the effects of a nurse led ICU follow up program (PRaCTICaL) failed to show any difference in health related quality of life (HRQL) between control and intervention groups at one year(14). In this study, 143 patients were randomized to a self-directed rehabilitation program. The authors outline several possible explanations for why the intervention did not improve HRQL, including the failure to integrate family in recovery, medical complexity requiring a multidisciplinary approach to this population (which PRaCTICal did not provide), and the timing of the intervention (too distant from hospital discharge). A Swedish post-ICU multidisciplinary follow-up clinic was implemented by Schandl et al but suffered from poor participation, a small sample size (N=61), and no controls(15). Patients were seen prior to hospital discharge and invited to come back at 3, 6, and 12 months after ICU discharge. Nearly a third died before the first follow-up visit, and a third of survivors declined follow up, resulting in very few complete interventions. Patients who declined follow-up had significantly higher comorbidity scores, suggesting that the individuals who needed it most did not receive the intervention. Petersson and colleagues offered a follow- up program based on three contacts during the 6 months following critical illness; half of these contacts occurred exclusively via telephone(16). Of the 96 patients enrolled, only 51% visited the outpatient nurse led clinic, and they were younger and healthier than those who did not follow up. This study's first outpatient visit was 2 months after discharge. No effectiveness data was reported.

In contrast to these negative findings, Khan and colleagues at the Indiana University School of Medicine recently reported on the results of their newly formed Critical Care Recovery Center (CCRC) and described positive outcomes from a total of 53 patients seen at their clinic between July 2011 and May of 2012(17). Patients were seen immediately after hospital discharge by members of a multidisciplinary team that included a physician, a nurse, a case manager, and a mental health professional, among others, and when deemed appropriate, were followed multiple times after their initial appointment. Among patients who were seen twice (N=24), statistically significant improvements were noted on a symptom checklist (Healthy Aging Brain Center Monitor – HABC-M tool) with a reduction in symptoms reported in cognitive ($p=0.04$) and functional ($p=0.02$) domains and with respect to overall symptoms ($p=0.01$); data were

analyzed in a simple univariate fashion. Of note is the fact that this study was done with a population of ***"high risk"*** patients who may be the subgroup of ICU patients most likely to benefit from a resource intensive post-ICU intervention.

ICU Recovery Clinic at Vanderbilt

In 2012, we developed a multidisciplinary ICU Recovery Clinic at Vanderbilt. Similar to the Indiana experience, our patients are unexpectedly young (mean age 55), survived a severe critical illness (mean SOFA score 10), and are markedly impaired. A third cannot walk unassisted at their first visit (an average of 30 days after hospital discharge), and more than half are cognitively impaired. For the last four years, the ICU Recovery Clinic has seen patients on an as-needed, by-referral basis, outside of the context of any structured ICU Recovery Program. With improving understanding of intense needs of ICU patients starting immediately at the time of ICU transfer and persisting through at least the first month of hospitalization, we have developed a 10-component multidisciplinary ICU Recovery Program which would provide multiple assessments and interactions with patients from the time of transfer out of the ICU to the hospital ward, between hospital discharge and clinic follow up, and during our ICU Recovery Clinic visit. We are planning to implement this 10-component ICU Recovery Program at Vanderbilt. The planned program, however, is resource-intensive and whether such a program is (1) feasible to implement and (2) improves patient-centered outcomes like 30-day hospital readmission will be important to know if such a program is to be sustained over the long term. Thus, we propose in the first 6 months of the ICU Recovery Program's implementation, to examine the delivery of each of the components of the intervention and the effect on 30-day readmission, in comparison to current usual care. To focus our ICU Recovery Program intervention on those patients most likely to benefit, we will target a population of ICU patients specifically felt to be at "high risk" of subsequent 30-day hospital readmission. Targeting "high risk" patients is important because these individuals have the greatest needs and the largest room to improve.

3.0 Rationale, Aims, and Hypotheses

An ICU Recovery Program may reduce 30-day same-hospital readmission rates and improve clinical outcomes and quality of life among adults recovering from critical illness. Development and implementation of an ICU Recovery Program, however, faces significant logistical challenges and the best model for providing care for survivors of critical illness remains unknown. Preliminary data on the feasibility and safety of developing and implementing an ICU Recovery Program are needed.

Primary Aim:

- To examine the feasibility of implementing a multidisciplinary ICU Recovery Program and the influence of such a program on process measures including contact with the ICU recovery team and attendance of ICU recovery clinic.

Secondary Aims:

- To compare the effect of a multi-disciplinary ICU Recovery Program versus usual care on the incidence of 30-day same-hospital readmission experienced by ICU survivors at high risk of readmission.
- To compare the effect of a multi-disciplinary ICU Recovery Program versus usual care on the hospital length of stay and 30-day mortality experienced by ICU survivors at high risk of readmission.

Primary Hypothesis:

- Implementation of a multidisciplinary ICU Recovery Program will be feasible and will increase contact with the ICU Recovery Team and attendance of the ICU Recovery Clinic.

Secondary Hypotheses:

- A multi-disciplinary ICU Recovery Program will decrease the incidence of 30-day same-hospital readmission experienced by ICU survivors at high risk of readmission compared with usual care.
- A multi-disciplinary ICU Recovery Program will not affect the hospital length of stay or 30-day mortality experienced by ICU survivors at high risk of readmission compared with usual care.

4.0 Study Description

To address the aims outlined above, we propose a pilot evaluation of an ICU Recovery Program for patients in the Vanderbilt MICU at high risk of readmission. Adult patients admitted to the Vanderbilt MICU with a high risk of readmission after hospital discharge who do not meet exclusion criteria will be enrolled and assigned to either

usual care or participation in an ICU Recovery Program. All other aspects of patients' care will be at the discretion of their treating providers. Data will be collected during the ICU admission, between ICU transfer and hospital discharge, and at 30 days after hospital discharge to determine the effect of the ICU Recovery Program on short- and long-term outcomes.

5.0 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria:

5. Age ≥ 18 years
6. Admitted to the Medical Intensive Care Unit (MICU) at Vanderbilt University Medical Center for at least 48 hours
7. Estimated risk of 30-day same-hospital readmission greater than 15%
8. Not previously enrolled in the study.

5.2 Exclusion Criteria:

1. Long-term residence at a skilled nursing facility
2. Long-term mechanical ventilation prior to admission
3. Solid organ or stem cell transplantation
4. Recorded primary residency > 200 miles from Vanderbilt
5. Comfort care only

Notes:
(1) Patients' estimated risk of 30-day same-hospital readmission are calculated currently as part of the Vanderbilt Office of Quality, Patient Safety and Risk Prevention Cornelius project which displays patients' estimate risk of 30-day same-hospital readmission with the electronic health record.
(2) Because enrollment occurs during the MICU admission and the ICU Recovery Program Intervention is delivered primarily after transfer out of the ICU, there will be patients enrolled who die before hospital discharge or are discharged with hospice care, such that they do not have an opportunity to receive the full study intervention. These patients will be enrolled and followed, but will not be analyzed in the primary 'per-protocol' analysis (see Statistical Analysis).

6.0 Enrollment/Randomization

6.1 Study Sites: Medical Intensive Care Unit at Vanderbilt University Medical Center

6.2 Study Population: All adults admitted to the MICU at VUMC for at least 48 hours with an estimated risk of 30-day same hospital readmission greater than 15% not

meeting exclusion criteria. Patients will be included regardless of gender, race, or other clinical factors.

6.3 Enrollment: All patients will be enrolled at the first time-point at which they meet all inclusion criteria without meeting exclusion criteria. Data on patient age, hospital location and admitting service, and risk of readmission are currently available for each patient in Vanderbilt's Electronic Health record. The acute care nurse practitioner and pharmacist in charge of the ICU Recovery Program will receive an automated report of these data daily and will determine by manual chart review whether eligible patients meet any exclusion criteria. For each eligible patient, the medical record number, date and time, and inclusion and exclusion criteria met will be recorded in a screening long housed within the secure, online database REDCap.

6.4 Consent:

The approach to post-ICU follow up in current routine care varies greatly by location, hospital system, and provider. Both usual care (in which the treating clinicians assist with healthcare transitions, medication reconciliation, and post-discharge follow up planning) and an ICU Recovery Program (in which a dedicated multidisciplinary team contributes to the same activities) are within the current standard of care. There are no randomized trials or evidence-based guidelines to support the choice of one approach to post-ICU follow up over the other. In many instances, the approach to post-ICU follow up a given patient receives depends on arbitrary factors unrelated to that patient (availability of an ICU Recovery Program at the hospital, insurance approval of post-ICU services, etc). Importantly, the nature of the ICU Recovery Program intervention imposes no additional health or safety risks to the patient above what they would experience in either usual care within the study or usual care outside of the study. We therefore feel the ICU Recovery Program presents minimal risk.

Vanderbilt's Office of Quality, Patient Safety and Risk Prevention has implemented the Cornelius program to automatically calculate at the time of hospital admission each patient's risk of 30-day same-hospital readmission. Currently at Vanderbilt, half of the patients have the risk score displayed in the electronic health record from the time of hospital admission to discharge, whereas for the other half the risk score is not displayed. Our evaluation of the ICU Recovery Program targeting patients at high risk of readmission relies on the Cornelius risk score and group assignment (generated at hospital admission). Obtaining informed consent prior to group assignment in the current evaluation of the ICU Recovery Program would require identifying and approaching at-risk ICU patients before hospital admission. Obtaining informed consent prior to group assignment would be impracticable.

Moreover, approaching patients for informed consent would introduce biases that could potential invalidate the study results. If patients were approached for informed consent before group assignment was generated (not possible due to

generation of group assignment for all patients at the time of hospital admission), two potential biases would be introduced:

- A patient or surrogate's willingness to consent in a study of ICU follow up would reasonably be expected to correlate with their likelihood of complying with ICU follow up interventions. Examining the effect of the ICU Recovery Program vs usual care only among a subgroup of patients who are more likely to comply with the intervention (and excluding a subgroup of patients less likely to comply with the intervention) falsely biases the towards demonstrating 'efficacy' of the intervention, a misleading result given that the goal is to assess the 'effectiveness' of the program as it would be applied across all ICU patients in usual care after implementation.
- Approaching patients for informed consent prior to group assignment would be anticipated to alter the care sought and received in the usual care group. Patients who are informed of the potential benefits for more intensive ICU follow up after critical illness and agree to participate in a study of a comprehensive ICU Recovery Program, who are then assigned to receive 'usual care', could reasonably be anticipated to more actively seek intensive ICU follow up (with their primary physician or even as a part of the ICU Recovery Clinic, which is available upon request to patients in the usual care group) than they would have been in true usual care. This would falsely limit separation between groups and bias toward a negative study because of a more active control group that true usual care.

If patients were approached for informed consent ***after*** group assignment, both of the above biases would remain present and an additional bias would be introduced: Patients might base the decision to participate on their group assignment. Patients might be overall more likely to participate in one group than the other causing selection bias, or patients who prefer more intense follow up might refuse participation in the usual care group and participate in the intervention group while patients who prefer less intense follow up refuse participation in the intervention group but not in the usual care group.

Because addition of an ICU Recovery Program to usual care (1) presents minimal risk and (2) would not adversely affect the welfare or privacy rights of the participants AND because obtaining informed consent would be impracticable both (3) due to the inability to approach prior to generation of study group assignment and (4) due to the risks of introducing systematic biases into the study findings, we will request a waiver of informed consent.

6.5 Randomization:

Since 2012, Vanderbilt's Office of Quality, Patient Safety and Risk Prevention displayed an estimated risk of 30-day same-hospital readmission for a random half of patients admitted to Vanderbilt University Medical Center. At the time of hospital admission, the Cornelius Quality Improvement Project randomizes patients 1:1 to either

display a risk of readmission to providers within the electronic health record or to not display a risk of readmission.

The risk score and group assignment generated at hospital admission by the Cornelius Quality Improvement Project will be used for the current study. Patients for whom a risk score is displayed in the electronic health record will be considered to be in the intervention group. Patients for whom a risk score is not displayed in the electronic health record will be considered to be in the control group.

7.0 Study Procedures

7.1 Study Interventions

USUAL CARE (Control)

Patients in the usual care group will receive care as dictated by their clinical team. In usual care in the study institution, patients frequently receive medication reconciliation by and ICU pharmacist at the time of transfer out of the ICU to the hospital ward, medication reconciliation by a physician at the time of hospital discharge, and follow up with their primary care physician within two weeks of hospital discharge. Usual care does not currently include an in-person assessment of the patient's cognitive and functional status or anticipated post-ICU needs by a nurse practitioner between ICU transfer and hospital discharge, access to a 24/7 contact line after hospital discharge, or assessment in a multi-disciplinary ICU Recovery Clinic.

VANDERBILT ICU RECOVERY PROGRAM (VIP) (Intervention)

In addition to the interventions received as a part of usual care, patients in the ICU Recovery Program group will receive a ***10-component ICU Recovery Program*** between ICU discharge and 30 days after hospital discharge, as outlined below.

PRIOR TO ICU RECOVERY CLINIC VISIT

Nurse Practitioner In-Person Visit. At the time of transfer from the ICU to the hospital ward, the ICU Recovery Program nurse practitioner will meet in person with the patient and family members. At this visit, the nurse practitioner will obtain a history of the patient's baseline cognitive and functional status, review the events of the patient's critical illness, and assess the patient's current and anticipated needs during recovery (***component 1***). Specific interventions at this visit will include:

- Scheduling request for an appointment in the ICU Recovery Clinic
- Provision of an ICU Recovery Program Pamphlet describing post-intensive care syndrome, details about the ICU Recovery Program services offered, and providing online resources (***component 2***)

- Provision of the phone number for the ICU Recovery Program contact line

Pharmacist In-Person Visit. At the time of transfer from the ICU to the hospital ward, the ICU Recovery Program pharmacist will review the patient's home medications, ICU course, and current medication regimen. Specific interventions at this visit will include:

- Performance of a formal medication reconciliation (***component 3***)

ICU Recovery Program Contact Line. From the time of transfer from the ICU to the hospital ward until 30 days after hospital discharge, the ICU Recovery Program Team will staff a dedicated 24-hour a day, 7-day a week contact line to serve as a "first call" for patients and their families following hospital discharge after critical illness (***component 4***).

DURING ICU RECOVERY CLINIC VISIT

Medical Examination. A structured interview will be conducted by a critical care nurse practitioner and will cover the patient's hospital course and any current physical problems or complaints. Data regarding weight change, smoking status, and alcohol intake will be collected. A focused physical with special emphasis on sequelae related to critical care (e.g., tracheostomy, respiratory failure, indwelling vascular catheters, weakness, skin breakdown) will be conducted. (***component 5***)

Medication Reconciliation and Counseling. A medication reconciliation and counseling intervention (***component 6***) will be conducted by a critical care pharmacist involving:

- A rapid review of medication discrepancies;
- A discussion of plans for filling new prescriptions;
- Anticipation and troubleshooting of barriers to adherence;
- Provision of adherence aids if appropriate.

Cognitive/Mental Health Assessment and Psychoeducation. A brief session of psychotherapy that includes a cognitive and mental health screening will be conducted by a clinical psychologist (***component 7***). Following screening, which will occur early in the session, there will be:

- A collaborative discussion using a validated "therapeutic assessment model" that highlights potential problems or areas of concerns based on the screening and
- Psychoeducation regarding potential post-discharge cognitive, mental health challenges, and family challenges, with focus on placing them in the context of "typical" ICU recovery as well as discussing what steps to take in the event that external referrals are needed.

Case Management. A brief case management consultation will be conducted by a nurse case manager (***component 8***). It will include linking the patient to relevant resources (e.g. community mental health, a fitness to drive assessment, etc), arranging for home care services and durable medical equipment as appropriate, and reviewing how to access resources such as after-hours clinics and express care. If the patient does not have a PCP, assistance will be provided in obtaining one in their insurance network, or in the community, if the patient is uninsured.

Patient Centered Consultation. A final consultation with patients and their families (who in virtually every case attend the clinic along with the patient) will be conducted by a PCCM physician to synthesize findings identified by other ICU Recovery Program team members, using a validated Patient Centered Consultation (PCC) approach that emphasizes communication, partnership, and health promotion (***component 9***). During this consultation, physiologic testing performed during the visit, including spirometry and the six minute walk test will be interpreted, and implications explained. New and persistent diagnoses, treatment plan, additional specialist referrals, and medication changes will be reviewed. Patients and family members will have an opportunity to ask questions. A survivorship care plan (SCP)126-130 based on those used in the cancer survivorship arena but tailored to address the unique needs of patients after critical illness will shared with the patient at this time. The SCP will include contact information for the care team, basic historic health information, detailed information about the patient's critical illness course, a list of medications, and specific recommendations for follow-up care with timelines.

AFTER ICU RECOVERY CLINIC VISIT

ICU Recovery Program Contact Line. From the time of transfer from the ICU to the hospital ward until 30 days after hospital discharge, the ICU Recovery Program nurse practitioners will staff a dedicated 24-hour a day, 7-day a week contact line to serve as a "first call" for patients and their families following hospital discharge after critical illness.

Directed Subspecialty Referrals. Following the ICU Recovery Clinic visit, additional subspecialty referral and ICU Recovery Clinic follow up may be scheduled based on the needs assessment developed for the patient during the clinic visit (***component 10***).

8.2 Data Collection

Baseline measures:

- Name, Medical Record Number, Date of Birth
- Age, gender, race, ethnicity
- Hospital admission date, ICU admission date

- Number of hospital admissions within the prior 12 months
- Height, weight, body mass index closest to admission
- Individual comorbidities, Charlson Comorbidity Index (CCI) Score
- Employment prior to hospitalization
- Tobacco use, Alcohol use prior to hospitalization

ICU Measures:

- Date of first ICU admission during hospitalization
- Active medial conditions prompting ICU admission; primary ICU diagnosis
- SOFA score on the first day of ICU admission
- Receipt of mechanical ventilation, duration of mechanical ventilation; receipt of non-invasive mechanical ventilation, duration of non-invasive mechanical ventilation
- Receipt of vasopressors, duration of vasopressor receipt
- Receipt of renal replacement therapy during the ICU admission, duration of renal replacement therapy receipt
- Delirium during ICU admission, receipt of continuous sedation during the ICU admission
- Date of initial ICU transfer during hospitalization, date of final ICU transfer during hospitalization

Post-ICU In-hospital Measures:

- In-person contact between patient/family and ICU Recovery Team nurse practitioner before hospital discharge; date of in-person contact
- Patient/family provided with ICU Recovery Team Letter and contact information; date ICU Recovery Team Letter and contact information provided
- Was patient scheduled for ICU Recovery Clinic Appointment, Date ICU Recovery Clinic Appointment scheduled
- If patient/family declined appointment, reason appointment was declined
- Ward service caring for patient after ICU admission
- Vital status at hospital discharge
- Date of hospital discharge
- Hospital discharge location
- Ambulatory status at hospital discharge

Post-Hospital Measures:

- *30-day same-hospital re-admission within 30 days of hospital discharge from the index admission (primary outcome).*
- Date of re-admission
- Vital status during follow up; date of last known vital status during follow up

- Number of same-hospital emergency department visits in the 30 days after hospital discharge

This project will utilize the REDCap platform for data collection and management. Project team members listed as Key Study Personnel with existing StarPanel access rights may also be granted use of REDCap Dynamic Data Pull (DDP) tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative into REDCap. The Research Derivative is a database of clinical and related data derived from the Medical Center's clinical systems and restructured for research. Data is repurposed from VU's enterprise data warehouse, which includes data from StarPanel, VPIMS, and ORMIS (Operating Room Management Information System), EPIC, Medipac, and HEO among others. The medical record number and other person identifiers are preserved within the database. Data types include reimbursement codes, clinical notes and documentation, nursing records, medication data, laboratory data, encounter and visit data, among others. Output may include structured data points, such as ICD 9 codes or encounter dates, semi-structured data such as laboratory tests and results, or unstructured data such as physician progress reports. The database is maintained by the Office of Research Informatics under the direction of Paul Harris, Ph.D.

8.3 Outcome Measures

Primary Endpoint:

Number of components of the ***ICU Recovery Program*** intervention received by patients between ICU transfer and 30 days after hospital discharge. The 10-components considered part of the **ICU Recovery Program** include: (1) nurse practitioner in-person visit between ICU transfer and hospital discharge, (2) ICU Recovery Program pamphlet, (3) pharmacist medication reconciliation at the time of ICU transfer, (4) ICU Recovery Program contact line, (5) nurse practitioner history and physical in ICU Recovery Clinic, (6) pharmacist medication reconciliation in ICU Recovery Clinic, (7) cognitive/mental health assessment and psychoeducation in ICU Recovery Clinic, (8) case management consultation in ICU Recovery Clinic, (9) patient centered consultation with PCCM physician in ICU Recovery clinic, (10), directed subspecialty referrals.

Secondary Endpoint:

30-day same-hospital readmission defined as the proportion readmitted to Vanderbilt University Medical Center in the 30 days following hospital discharge.

Tertiary Endpoints:

- Days alive and free of same-hospital readmission in the 30 days after hospital discharge (re-admission free days)
- Composite of death or readmission in the 30 days after hospital discharge

- Number of same-hospital emergency department visits in the 30 days after hospital discharge
- Number of same-hospital outpatient clinic visits in the 30 days after hospital discharge
- Number of referrals to specialty providers in the 30 days after hospital discharge

8.0 Risks and Benefits:

For ICU patients at high risk of readmission, there are currently no established risks or benefits to the addition of an ICU Recovery Program to usual care. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients as a part of routine care outside of the study. The greater benefit of the study would be to society in the form of improved understanding of the optimal approach to post-ICU follow up.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

9.0 Safety Monitoring and Adverse Events:

9.1 Safety Monitoring

Given the nature of the ICU Recovery Program intervention (increased contact with a critical care nurse practitioner, pharmacist, and physician) during the hospitalization and after discharge, there are no specific safety events anticipated to arise from the intervention. Nonetheless, study personnel blinded to group assignment will monitor the records of all participants for 30 days after hospital discharge to formally determine the presence of any safety events related to the study. Study personnel will be readily available to answer questions at any time during the study course. If, at any point during the study, a clinical provider feels an alternative approach to post-ICU follow up is required for the safe treatment of the patient, the post-ICU follow up will be managed in the manner the treating clinician judges to be safest.

9.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation participant administered an intervention that does not necessarily have to have a causal relationship with this treatment. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the

use of an intervention, whether or not the incident is considered related to the intervention.

A serious adverse event (SAE) is defined as any unexpected and untoward medical occurrence that meets any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death if it would have been more severe)
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigators will be responsible for overseeing the safety of this study on a daily basis. They will be available at any time for questions from the bedside physicians and nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events during the hospitalization. Serious and unexpected adverse events associated with study interventions will be recorded in a case report form in the study record and reported to the IRB within 7 business days. As critical illness requiring ICU admission is independently associated with numerous adverse events (irrespective of the approach to post-ICU follow up) including death, cardiac arrest, hemodynamic or respiratory failure, ICU readmission, hospital readmission, and prolonged cognitive or physical impairment, these events are expected in the routine care of critically ill adults and will not be individually recorded and reported to the IRB as unexpected serious adverse events.

10.0 Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- The treating clinician decides the patient should be withdrawn for any reason.
- The patient or surrogate decision makers decides the patient should be withdrawn for any reason.
- There is a significant protocol violation in the judgment of the primary investigator.

The reason for and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will

be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

11.0 Statistical Considerations

Original Sample Size Determination (3/22/17):

In the six months prior to the design of the pilot, there were 1,602 admissions to the Vanderbilt Medical ICU, 340 (21.2%) of whom experienced the primary outcome of 30-day same-hospital readmission. Of the 1,602 admissions, 672 (41.9%) had a predicted risk of readmission at least 25% at the time of ICU admission, 189 (28.1%) of whom experienced the primary outcome of 30-day same-hospital readmission.

This pilot ICU program will have adequate support for the nurse practitioner and bioinformatics staff to run for 6 months. Based on this fixed duration, we anticipate the number of patients enrolled in this pilot study to be around 650. We anticipate that around 15% of patients will be ineligible for participation in the ICU Recovery Program due to death in the ICU or transition to hospice, leaving around 550 patients who will receive either usual care or the ICU Recovery Program. Assuming a rate of the primary outcome in the usual care group of 28%, 550 total patients will allow us 80% statistical power at an alpha level of 0.05 to detect an absolute reduction in the primary outcome of around 10%, comparable to a relative risk reduction of 35%.

Revised Sample Size Determination (6/12/17):

In the six months prior to the design of the pilot, there were 1,602 admissions to the Vanderbilt Medical ICU, 340 (21.2%) of whom experienced the primary outcome of 30-day same-hospital readmission. Of the 1,602 admissions, 1,236 (77.2%) had a predicted risk of readmission greater than 15% at the time of ICU admission, 272 (22.0%) of whom experienced the primary outcome of 30-day same-hospital readmission.

This pilot ICU program will have adequate support for the nurse practitioner and bioinformatics staff to run for 6 months. The enrollment target for the study is a total of 650 patients, which (anticipating that around 15% of patients will be ineligible for participation in the ICU Recovery Program due to death or transition to hospice) will allow a total of 550 patients to receive either usual care or the ICU recovery program. After the first month of the trial, in order to achieve the planned enrollment target, the study team recognized that the actual rate of enrollment using the initially specified risk score of 25% would be inadequate to meet the planned enrollment of 550 patients. The risk score required for inclusion was therefore decreased to >15%.

Assuming a rate of the primary outcome in the usual care group of 22%, 550 total patients will allow 80% statistical power at an alpha level of 0.05 to detect an

absolute reduction in incidence of the 30-day readmission of 10%, comparable to a relative risk reduction of 45%.

Statistical Analysis:

Pilot study profile:

We will present a Consolidated Standards of Reporting Trials diagram as Figure 1 to detail the movement of patients through the study. This diagram will include total number of patients meeting inclusion criteria, number excluded and reason for exclusion, number enrolled and randomized in the study, number followed, and number analyzed.

Baseline Characteristics:

To assess randomization success, we will summarize in Table 1 the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and percentages and continuous variables as either means with SDs or medians with interquartile ranges. Variables reported will include Demographics (age, gender, race, BMI); Comorbidities; Pre-admission location; ICU admitting diagnosis; receipt of vasopressors and mechanical ventilation; and severity of illness.

Primary Analysis: The primary analysis will be an unadjusted comparison of the proportion of patients who receive an any ICU Recovery Program intervention in the usual care and ICU Recovery Program groups, among patients discharged from the hospital alive to a non-hospice location ('modified intention-to-treat') using a chi-square test. *Enrolled patients who die in the ICU, die between ICU transfer and hospital discharge, or who are discharged from the hospital to hospice will not be included in the primary analysis.*

Secondary Analyses:

Intention-to-treat analysis

We will perform an unadjusted comparison of the proportion of patients who receive an any ICU Recovery Program intervention in the usual care and ICU Recovery Program groups, among all enrolled patients ('intention-to-treat') using a chi-square test. *Enrolled patients who die in the ICU, die between ICU transfer and hospital discharge, or who are discharged from the hospital to hospice will be included in this secondary analysis.*

Modified Intention-to-treat analysis of secondary and tertiary outcomes

We will conduct an unadjusted analysis examining the effect of the ICU Recovery Intervention versus usual care on the pre-specified secondary and tertiary outcomes

including 30-day same hospital readmission, among those patients discharged from the hospital alive to a non-hospice location.

Per-Protocol Analysis of Primary Outcome in the modified intention-to-treat population.

We will test the hypothesis that receipt of the full ICU Recovery Program intervention is associated with lower 30-day same hospital readmission by comparing the incidence of 30-day same-hospital readmission between patients who received all component of the ICU Recovery Program intervention and those who did not receive all components of the ICU Recovery Program intervention, among those patients discharged from the hospital alive to a non-hospice location.

Subgroup Analyses.

We will conduct unadjusted analyses examining the effect of the ICU Recovery Program versus usual care on 30-day same-hospital readmission in each of the pre-specified subgroups using a formal assessment of statistical interaction. Data will be presented as odds ratios and 95% confidence intervals for categorical variables and as mean differences and 95% confidence intervals for continuous variables.

Modeling to Examine Potential Confounding Factors.

We will develop a multiple regression model with 30-day same-hospital readmission as the dependent variable and study group and relevant confounders included as independent variables.

Presentation of Statistics

Continuous variables will be described as mean and standard deviation or median and 25th percentile – 75th percentile or bootstrapped 95% confidence intervals as appropriate. Categorical variables will be given as percentage and number. All between-group comparisons with continuous variables will be performed using Mann-Whitney U tests and chi-square or Fisher's exact test for categorical variables. Kaplan-Meier curves and log-rank tests will be used to analyze time-to-event comparisons between groups.

12.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database Redcap. All data will be maintained in the secure online database Redcap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

13.0 Follow-up and Record Retention

Patients will be followed for 30 days after hospital discharge. Data collected from the medical record will be entered into the secure online database Redcap. Once data is verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database Redcap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

14.0 References

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