Protocol #:

TITLE: IMPROVING MORBIDITY DURING POST ACUTE CARE TRANSITIONS FOR SEPSIS (IMPACT SEPSIS): A PRAGMATIC RANDOMIZED EVALUATION OF IMPLEMENTING BEST PRACTICE CARE FOR SEPSIS SURVIVORS TO REDUCE MORBIDITY AND MORTALITY

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

PROTOCOL SUMMARY	
Study Title	Improving Morbidity during Post Acute Care Transitions for Sepsis (IMPACT Sepsis): A Pragmatic Randomized Evaluation of Implementing Best Practice Care for Sepsis Survivors to Reduce Morbidity and Mortality
Study Design	A pragmatic, randomized program evaluation
Study Objectives	The primary objective is to evaluate the composite of all cause, 30-day hospital readmissions and post-discharge mortality between usual care and care delivered through Sepsis Transition and Recovery (STAR) program. The secondary objectives are to separately evaluate the effects of STAR on the individual components of the composite outcome (i.e., hospital readmissions, mortality) and other patient outcomes (e.g., ED visits, cost).
Study Population	Adults admitted through the emergency department with suspected serious infection (i.e., antibiotics initiated, bacterial cultures drawn) and deemed to be at high risk for readmission or death.
Study Procedures	A STAR nurse navigator will receive a daily list of admitted patients eligible for the STAR program. Eligible patients will be randomized 1:1 to STAR program or usual care. The STAR navigator will provide telephone- and EHR-based support to patients within their hospitalization and across all discharge settings for30 days using targeted, evidence-based best-practice care components: i) identification and appropriate referral for new physical, mental, and cognitive deficits; ii) comprehensive review and adjustment of medications; iii) post-discharge surveillance for treatable conditions that commonly lead to poor outcomes; and iv) focus on palliative care when appropriate. The STAR navigator will also help coordinate provider follow-up appointments and refer for escalation of care as necessary (e.g., primary care provider, transition services, community paramedicine).
Sample Size Estimates	Group sample sizes of 354 in the STAR group and 354 in the usual care group achieve 80% power to detect a difference between the group proportions of -0.10 (relative difference = -0.25). The proportion in the control group is 0.40, and the proportion in the treatment group is assumed to be 0.30 under the alternative hypothesis. The test statistic used is the two-sided Z-Test with unpooled variance and the significance level is 0.05.
Statistical Analyses	We will use an intent-to-treat approach to primary and secondary analyses, such that all patients meeting identical criteria and randomized will be analyzed, regardless of adherence to intervention assignment. We will use a logistic regression model to compare the composite 30-day mortality and readmission primary outcome measure between the intervention conditions. We will present results from group comparisons as odds ratios and 95% confidence intervals.

TABLE OF CONTENTS

1. Objectives

1.1 Primary Objective

The primary objective of the IMPACT Sepsis evaluation is to compare the composite of all-cause 30-day hospital readmissions and post-discharge mortality between care delivered through the Sepsis Transition and Recovery (STAR) program and usual care.

1.2 Hypothesis

Patients referred to the STAR program will have a lower composite all-cause 30-day hospital readmissions and post-discharge mortality rate than patients who receive usual care.

1.3 Secondary Objectives

The secondary objectives are to evaluate the STAR program's effects on specific patient outcomes, processes, and costs including:

- All-cause 30-, 60-, and 90-day hospital readmission rate
- All-cause 30-, 60-, and 90-day post-discharge mortality rate
- All-cause emergency department visits within 30, 60, and 90 days of discharge
- Total 30-, 60-, and 90-day acute care costs
- Total 30-, 60-, and 90-day healthcare costs (*only subset of population with Medicare Shared Savings Plan insurance coverage)
- Cause-specific 30-day hospital readmission rates for a) infection, b) chronic lung disease, c) heart failure, and d) acute kidney injury
- 30-day acute care-free days alive, defined as the sum of days alive without inpatient, observation, and emergency department encounters during the 30 days after discharge

We will report the percentage of patients with documentation of the following process measures: 1) inpatient functional assessment or physical therapy consult; 2) mental health assessment by PHQ-2 or PHQ-9 before discharge; 3) referrals to physical therapy or outpatient rehabilitation, speech therapy, and behavioral health; 4) outpatient follow-up within 7 days of discharge; and 5) documented medication reconciliation in the EHR during the 30 days post-discharge. Because sepsis may occur in the setting of long-standing illness and declining health which frequently results in death,[1-3] we will measure quality of end-of-life care, including place of death (i.e., hospital or other location) and the proportion who received palliative care consult, completed care preferences documentation, and discharged to hospice.

2. Background

Gaps in post sepsis care lead to persistently high morbidity and mortality. Sepsis is a common and life-threatening condition defined by organ dysfunction due to a dysregulated response to infection. Worldwide in 2016, sepsis afflicted over 19 million patients and caused more than 5 million deaths.[4] Aggressive early sepsis identification and treatment initiatives such as the Surviving Sepsis Campaign have decreased in-hospital mortality for patients with sepsis over the last two decades.[5-7] However, little has been done to address the downstream effects of sepsis for the approximately 14 million annual sepsis survivors who encounter increased long-term mortality and morbidity across functional, cognitive, and psychological domains. Following an episode of sepsis, three-quarters of patients 65 and older develop new functional disabilities with an average of 1-2 new impairments.[7] One-sixth of older patients develop moderate to severe cognitive impairment, and post-

sepsis patients are more than twice as likely to progress to dementia than non-hospitalized patients.[7-9] Sepsis survivors frequently experience clinically significant anxiety, depression, and post-traumatic stress disorder.[10-12] Sepsis survivors with comorbidities such as heart failure or chronic lung disease frequently experience exacerbations of these conditions after recovering from sepsis.[13] The increasing incidence of sepsis survivors coupled with high rates of long-term comorbidities creates an urgent public health challenge.[14,15] Currently, there is a disconnect between the post-acute care needs of sepsis survivors and the resources available to these patients. Sepsis survivors report only low to moderate satisfaction with support services provided after discharge, and they experience a notable lack of timely post-discharge follow-up.[16-19] The inadequate post-sepsis care strategies are reflected by increased mortality risk and strikingly high rates of healthcare utilization including a 90-day hospital readmission rate of 40%, resulting in over 3 billion dollars in preventable costs.[20-24] These findings indicate further research is needed to determine successful implementation strategies for post-sepsis transitions after initial hospitalization.

Current evidence suggests that outcomes can be improved for sepsis survivors using coordinated, proactive measures. Over 40% of hospital readmissions after sepsis have been shown to result from preventable causes.[13] To address the specific treatment gaps for sepsis survivors, international experts developed best-practice recommendations to guide delivery of post-sepsis care.[25] These best-practice recommendations are directed towards the specific challenges and sequelae following a sepsis hospitalization and include: i) identification and treatment of new physical, mental, and cognitive deficits; ii) review and adjustment of medications; iii) surveillance for treatable conditions that commonly lead to poor outcomes; and iv) focus on palliative care when appropriate.

Best-practice recommendations for post-sepsis care are infrequently applied, with our own healthcare system's data indicating that recommended care is provided for less than half of sepsis patients. Although recommendations for post-sepsis practices to improve outcomes exist, their implementation is hindered by a gap in understanding how to best implement and disseminate interventions in the complex and fragmented post discharge setting. Common barriers to adoption of evidence-based-practice across the transition from the acute care setting include fragmented care delivery, lack of provider time and patient engagement, limited access to care management, and insufficient institutional support.[26-30] However, there are important recent quality and cost incentives that encourage healthcare systems to direct resources and attention toward overcoming these barriers. Improving care transitions and reducing 30-day hospital readmissions are important to patients and are high priorities for US healthcare providers.[31-34] Hospitals now face financial penalties imposed by Centers for Medicare and Medicaid Services (CMS) Hospital Readmission Reduction Program (HRRP) for higher-than-expected readmission rates for targeted conditions (i.e., chronic lung disease, pneumonia, heart failure, myocardial infarction, knee and hip replacements, coronary artery bypass graft surgery).[35,36] Because sepsis accounts for a larger proportion of all readmissions than any other index hospitalization diagnoses, experts have argued that sepsis hospitalizations should also be included in the CMS HRRP.[37] Further, new payment models, such as bundled payments and shared savings programs for Accountable Care Organizations, also create incentives to improve transitions and deliver care in less intensive settings during the interval after sepsis hospitalization.[38]

3. Rationale

Developing an implementation strategy to improve care and health outcomes for sepsis survivors. In randomized controlled trials (RCTs), including our previous work, successfully implemented care transition programs using nurse navigators have been shown to reduce readmissions and costs.[39-43] To better enhance transitions of care for the highest risk, complex patients with suspected sepsis, we propose extending this evidence using a nurse-facilitated care transition program for patients in the post-sepsis transition period to

improve the implementation of recommended care practices and bridge care gaps. This approach, called the Sepsis Transition and Recovery (STAR) program, is the next step in the progression of our group's work on improving discharge transitions and sepsis processes of care. A key aspect of this initiative includes the ability to identify sepsis survivors at the greatest risk for poor outcomes. For example, one-quarter of sepsis survivors account for three-quarters of readmissions and cost, indicating that identifying high-risk sepsis patients for targeted facilitation of best-practice care could efficiently impact quality and cost.[21]

Our STAR program uses near real-time risk modeling to identify high-risk patients and a centrally located nurse, virtually connected to participating hospitals, to coordinate the application of evidence-based recommendations for post-sepsis care, overcome barriers to recommended care, and bridge gaps in service that can serve as points of failure for complex patients.[44] During their hospitalization, high-risk patients enter into a transition pathway that includes the following core components:

(i) Introduction to STAR process prior to discharge (confirm provider consults e.g., PT, ID, palliative)
(ii) Disease-specific education and discharge "playbook"
(iii) Virtual hospital follow-up evaluation within 48 hours including medication reconciliation
(iv) Second, post-acute virtual follow-up within 72 hours (symptom monitoring, confirm provider follow-up)
(v) Weekly contact with care management team
(vi) Referral to provider follow-up (e.g., PCP, transition clinic) as appropriate
(vii) Coordinated transition to the next appropriate care location after 30 days from time of discharge

The IMPACT Sepsis (Improving Morbidity during Post Acute Care Transitions for Sepsis) evaluation will examine if implementation of the STAR program within a large healthcare system will improve outcomes for high-risk sepsis patients. This randomized program evaluation is designed to be a seamless part of routine care in a real-world setting to generate knowledge of best practices for implementation and dissemination of post-sepsis transitions of care.

4. Investigational Plan

4.1 Overall Study Design

This real-world pragmatic randomized program evaluation will compare the effectiveness of the Sepsis Transition And Recovery (STAR) program versus usual care on post-sepsis care and patient outcomes. The STAR program is informed by existing evidence and designed using the Chronic Care Model to increase best-practice adherence and care coordination, resulting in improved transitions between hospitals and post-acute care during sepsis recovery.

Because of resource limitations, STAR can only be made available to a limited number of patients. To be objective in patient selection and allow for program evaluation, we will use a data driven approach to identify patients as eligible for program referral. First, risk modeling will identify patients as high risk for 30-day readmission or 30-day mortality during the first day of the hospital admission. Then from this pool of high-risk patients, up to 6 patients will be randomly selected each weekday to be referred to either receive usual care or care delivered through the STAR program. The number of daily patients to be randomized was selected to match targeted capacity for the STAR navigator and will be reevaluated on a biweekly basis. Because variables that affect eligibility may change during a hospital stay, initial eligibility will be re-confirmed at time of hospital

discharge. Specifically, patients who have had infection diagnosis ruled-out during their hospitalization (i.e., rule-out documented in medical record) will be excluded for the purposes of analysis. All remaining eligible patients at the time of discharge will be included in analyses, which will be conducted using an intent-to-treat approach. Planned enrollment is 708 patients (n=354 patients per study arm) and STAR program follow-up will be completed 30 days after hospital discharge. Outcomes data will be tracked for 90 days and captured from routinely collected data from the Atrium Health Enterprise Data Warehouse. Given this evaluation protocol is part of a quality improvement intervention that relies on using evidence-based interventions, only utilizes data collected as part of routine care, and is minimal risk to patients, we requested that the institutional review board designate this study as expedited research and grant a waiver of informed consent.

4.1.1 Primary Outcome Variable

The primary outcome is a composite, dichotomous endpoint of all-cause mortality or unplanned hospital readmission assessed 30 days post index hospital discharge. This combined outcome is ideally suited to the proposed pragmatic study design because the elements are uniformly captured from data contained in the Atrium Health enterprise data warehouse, minimizing non-differential assessment, outcome misclassification, and missing data. Additionally, mortality and hospital readmission are widely regarded as patient-important outcomes, and rates for both adverse outcomes remain high after sepsis hospitalization.[37,45,46] Preventing avoidable hospital readmissions has been targeted as a high priority for health care reform in the United States and represents a critical quality metric for hospitals.[35] Readmission rates have recently declined secondary to focused initiatives.[47] However, some data suggest increased mortality during the same interval,[48] indicating the importance of measuring mortality and readmission rates in combination.

Mortality will be defined as any date of death documented in the Atrium Health enterprise data warehouse within 30 days of index hospital discharge. This includes data from 1) index inpatient death; 2) date of death after index hospital discharge documented in the EHR (captured electronically in the enterprise data warehouse); and 3) date of death records from the Social Security Death Master File with routine monthly data feeds to the enterprise data warehouse. Readmission will be defined as any unplanned inpatient or observation encounter to any Atrium Health hospital within the 30 days following index hospital discharge. This information will be captured from encounter data in the Atrium Health enterprise data warehouse, as has been done by the study team previously.

4.1.2 Secondary Outcome Variables

Secondary clinical outcomes: We will assess individual components of the primary outcome composite, i.e., 30-day hospital readmission and mortality. We will also track additional healthcare utilization measures: 1) unplanned all-cause emergency department visits without hospital admission within 30 days of discharge; 2) outpatient provider visits; 3) cause-specific hospital readmissions with primary diagnoses related to: a) infection, b) chronic lung disease, c) heart failure, and d) acute kidney injury; 4) hospital length of stay; and 5) 30-day acute care-free days alive, defined as the sum of days alive without inpatient, observation, and emergency department encounters (rounded to full day for any day with acute care utilization) during the 30 days after discharge. First, the total potential follow-up time will be calculated as the number of days from index discharge to the earliest date of death or 30 days post-discharge (patients who die during their index hospitalization will have zero days alive). Each potential follow-up day will be categorized as either an acute care day or acute care-free day, based on any inpatient, observation, or emergency department encounter on that day. Total acute care-free days alive will be calculated as the total potential follow-up time minus the number of acute care days during the 30 days after index hospital discharge.

Process measures: To provide additional context to understanding STAR implementation, we will track important process measures in both groups including:1) functional assessment or physical therapy consult; 2) mental health assessment by PHQ-2 or PHQ-9; 3) referrals to physical therapy or outpatient rehabilitation, speech therapy, and behavioral health; 4) completed (i.e., arrived) outpatient primary care follow-up within 7 days of discharge; and 5) documented medication reconciliation in the EHR during the 30 days post-discharge. Because sepsis may occur in the setting of long-standing illness and declining health,[1-3] we will measure quality of end-of-life care, including place of death (i.e., hospital or other location) and the proportion who received palliative care consult, completed care preferences documentation, and discharged to hospice.

Cost measures: These data will provide benchmarks to inform health policy decisions and resource allocation for post-sepsis care. We will define total incremental costs as costs associated with the STAR program services (e.g., dedicated program staff - navigator, training) plus acute care and total costs of healthcare services received over the 30-day follow-up. We will build a generalized linear model, using the gamma distribution and log-link function due to the skew of cost data. Total cost per patient will be the dependent variable and the assigned treatment (i.e., usual care, STAR) will be the primary independent variable.

4.2 Subject selection

Consistent with our pragmatic study design concept, eligibility criteria are broad and study procedures are embedded into the context of routine care. Subject selection will occur via an automated query process for patient list generation. Each weekday morning, actively admitted patients at 3 study hospitals (i.e., Carolinas Medical Center, Carolinas Medical Center – Mercy, and Atrium Health Northeast) will be identified from the electronic medical record and Enterprise Data Warehouse and output into daily eligibility lists. Lists are generated based on the following criteria:

4.2.1 Inclusion Criteria

(1) Admitted from the emergency department to inpatient or observation status at one of: Carolinas Medical Center, Carolinas Medical Center – Mercy, or Atrium Health Northeast;
(2) ≥18 years of age upon admission;
(3) oral/parenteral antibiotic or bacterial culture order within 24 hours of emergency department presentation and
  (a) culture drawn first, antibiotics ordered within 48 hours or
  (b) antibiotics ordered first, culture ordered within 48 hours (adapted from criteria applied in development of the Third International Consensus Definitions for Sepsis and Septic Shock)
(4) deemed as high-risk for 30-day readmission or 30-day mortality using risk-scoring models.

4.2.2 Exclusion Criteria

(1) Prior randomization to either STAR or usual care study arms;
(2) Not a North Carolina resident or residence >2.5-hour drive time from treating hospital;
(3) the only antibiotic associated with patient is administered in the operating room as this likely represents pre-operative infection prophylaxis and not presumed infection;
(4) patients transferred from other acute care hospitals;
(5) patients with a change in code status (i.e., do not resuscitate, do not intubate) within 24 hours after admission due to the general assumption of increased risk of exposure to less aggressive treatment;
(6) patients with infection ruled out during the index hospitalization;

(7) patients enrolled in Transition Services at time of index hospital discharge (for modified intention-to-treat analysis only);
(8) patients who die during index hospitalization or discharged against medical advice (for subgroup analysis only).

4.3 Randomization

Patients who meet eligibility criteria will be randomized into one of two study groups (i.e., usual care or STAR). A constrained randomization scheme will be utilized to randomly allocate up to 6 eligible patients to either STAR or usual care each day. The total allocation is based on estimated capacity for the STAR navigator. Allocation will be 1:1 STAR vs usual care.

4.4 Study Procedures

Each morning (Monday through Friday) the list of eligible patients will be automatically generated. Patients will be randomly assigned to STAR and usual care arms. For those patients allocated to receive care via STAR, their information will populate a list, which will be sent via secure e-mail to the STAR navigator. Patients in both arms will be entered into the study database for tracking. At any point, the patient may decline participation in STAR or any components of usual care.

Patients in the usual care group will continue to receive usual care throughout their stay and discharge, which are not prescribed but may consist of: patient education and follow-up instructions at discharge,; routine recommendations for follow-up visits with primary care providers; arrangements for home health services or care management follow-up based on each patient's needs but not specifically tailored to the sepsis population; and discharge to post-acute setting but with no sepsis-specific follow-up. Consistent with the concept of a pragmatic RCT, aspects of usual care will be determined by treating clinicians independent of trial assignment.

Patients in the intervention arm will receive care via the STAR program. The STAR program will employ a centrally located nurse navigator as part of Atrium Health Ambulatory Care Management, integrated with Atrium Health Transition Services, and connected virtually to all participating hospitals and resources (e.g., Atrium Health phone, messaging, and EHR systems). The STAR navigator will provide proactive coordination and monitoring for patients using targeted, evidence-based best-practice care components: i) identification of and referral for new physical, mental, and cognitive deficits; ii) review and recommendation for adjustment of medications; iii) surveillance for treatable conditions that commonly lead to poor outcomes; and iv) referral to palliative care when appropriate. The STAR navigator will provide telephone- and EHR-based support within the hospitalization staying in contact with the patient or caregiver as appropriate and hospital-based providers. Following discharge, the STAR navigator will follow patients regardless of discharge location remotely monitoring via EHR review and telephone at specified intervals throughout the 30 days post hospital discharge. We will partner with Chief Medical Officers and Nursing Executives at each facility to engage frontline staff, provide initial STAR program education, and conduct bimonthly touchpoints. Because the patient-facing intervention is designed to be delivered via telephone, patients do not require special equipment or training. At the initial telephone-based contact with the patient or caregiver during hospitalization, the STAR navigator will introduce the STAR program and(in situations when patient can participate) conduct health literacy screening and mental health screening using the Patient Health Questionnaire (PHQ)-2, with reflex administration of PHQ-9 for positive PHQ-2 (i.e., $\geq$3 points on 0-6 point scale).[49] The STAR navigator will ensure results are communicated to the patient's attending physician.

Additionally, the STAR navigator will confirm consultations with physical therapy (with recommendations delivered to care team), antibiotic stewardship (i.e., a coordinated program that promotes appropriate antibiotic use) with additional infectious disease consult if ongoing Systemic Inflammatory Response Syndrome criteria more than 48 hours after infection onset (i.e., abnormal body temperature, heart rate, respiratory rate, white blood cell count), and palliative care team as appropriate. Before discharge, the STAR navigator will provide infection-specific education to the patient and caregiver, which will also include what to expect during transition from the hospital and a "playbook" with information on planned follow-ups. The playbook will highlight all scheduled or planned in-person and phone follow-up touchpoints.

Irrespective of discharge location (e.g., home versus skilled nursing facility), the STAR navigator will provide telehealth monitoring at <48 hours, 72-96 hours, and 7-10 days post-discharge. These touchpoints will include medication reconciliation, targeted symptom monitoring, vitals and weight checks, and confirmation that the patient can make scheduled outpatient appointments. Concerns identified through proactive monitoring will prompt a primary care provider contact for follow-up. If the primary care provider cannot be reached after one attempt, the navigator will contact Atrium Health Transition Services. Following the immediate post-acute interval, the STAR navigator will maintain weekly telehealth touchpoints with patients who remain at high-risk for poor outcome (i.e., any previous positive screen, high-risk comorbid condition [e.g., chronic lung disease, heart failure],[13,50-52] or low health literacy[53]) and one additional third week touchpoint with patients considered low-risk after the immediate post-acute interval. Each of these post-acute touchpoints will include targeted symptom check, vitals and weight monitoring, and escalation to an additional outpatient provider visit if there are concerns. Any identified concerns will again prompt an attempt to contact the primary care provider followed by Atrium Health Transition Services. The STAR program will complete 30 days post hospital discharge with the patient transitioned to the next appropriate care setting.

4.5 Statistical Analysis

4.5.1 Sample Size Determination

This study is designed to detect a 25% relative reduction in the primary outcome, composite rate of 30-day readmission and mortality, which is reasonable given prior literature suggesting 22% and 42% of hospital readmissions after sepsis are preventable. Based on the historical data, the control group is estimated to have a 40% combined readmission and mortality rate. Group sample sizes of 354 in the STAR group and 354 in the usual care group achieve 80% power to detect a difference between the group proportions of -0.10 (i.e., 25% relative reduction). The proportion in the STAR group is assumed to be 30% under the alternative hypothesis. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.05.

4.5.2 Statistical Methods

All analyses will follow an intent-to-treat approach such that patients will be analyzed based on the group to which they were initially randomized after reapplication of inclusion and exclusion criteria at the time of hospital discharge (discharge eligible). We will assess the balance in the distributions of baseline characteristics (age, gender, race, comorbidities) between study groups. Comparisons of the two groups will be made using univariate analyses such as the t-test and chi-square test.

The primary outcome, composite readmission and mortality in 30 days, will be compared between the two groups of patients who are discharge eligible using logistic regression. We will evaluate covariates for patient (e.g., sex, race, comorbidities, length of stay, discharge disposition [skilled nursing facility, rehabilitation, home]) and organizational factors (e.g., admitting hospital) to identify any potential differences between study

arms. We will present results from group comparisons as odds ratios and 95% confidence intervals. In addition to the primary intent-to-treat analysis and since there is significant overlap between general Atrium Health Transition Services and the STAR program services integrated within Atrium Health Transition Services, we will conduct a modified intent-to-treat analysis excluding usual care patients enrolled in Transition Services at time of index hospital discharge. Based on historical data, we anticipate an approximately 10% referral rate to Transition Services in the usual care group. Also, since the STAR program is intended to support patients through the transition from the index hospitalization, we will conduct a subgroup analysis of patients who survived index hospitalization and were not discharged against medical advice. Finally, we do not anticipate substantial missing data because all outcomes are routinely collected variables and utilization is broadly captured within the large integrated system. While utilization may occur outside of Atrium Health, this is not expected to be a major limitation because of Atrium Health market share and accessibility. Specifically, Atrium Health operates three large hospitals in Cabarrus and Mecklenburg Counties and more than 40 hospitals in the region overall. Additionally, any utilization that occurs outside the system is anticipated to be non-differentially distributed between groups and thus impact treatment groups equally. Further, internal data indicates nearly 75% of high-risk patients are Medicare-insured (i.e., Medicare Shared Savings Plan beneficiaries) and have complete healthcare claims within and outside Atrium Health facilities captured through participation in the Accountable Care Organization managed by Atrium Health. We will conduct a subgroup analysis of this Medicare-insured population and use this data to explore missing data patterns that can be adjusted using pattern-mixture methods in sensitivity analyses.

Secondary outcomes, acute care and total costs, and process measures will be evaluated using the same approach. We will test different distribution parameters to determine the optimal distribution family for each model and outcome variable (e.g., gamma distribution for costs, Poisson for acute care-free days). All hypothesis tests will be two sided and data will be analyzed using SAS Enterprise Guide v7.1 (Cary, NC), R v3.5 (Vienna, Austria) or STATA v15 (College Station, TX).

5. Study Governance

This randomized program evaluation will be conducted at three tertiary acute care hospitals: Carolinas Medical Center, Carolinas Medical Center – Mercy, and Atrium Health NorthEast. It will be run jointly by the Center for Outcomes Research and Evaluation (CORE), Internal Medicine Department, and Ambulatory Care Management. Marc Kowalkowski, PhD (CORE) and Stephanie Taylor, MD (Internal Medicine) will serve as Principal Investigators with oversight from the Executive Committee. The Executive Committee will consist of leaders across the System involved in the trial, quality improvement, and STAR program implementation. The Executive Committee will have the overall responsibility of trial oversight and direction. The Executive Committee will support dissemination of project findings and next steps. The Executive Committee will receive monthly progress reports and will meet on a quarterly basis for status updates from the study team and to set direction. When appropriate, ad hoc committee meetings will be scheduled to discuss immediate concerns.

IMPACT Sepsis Executive Committee	
Scott Furney	Internal Medicine Academic Department
Scott Lindblom	Senior Medical Director, Internal Medicine Adult Acute Division
Ryan Brown	Medical Director, Carolinas Hospitalist Group
John Barkley	VP & Chief Medical Officer, Continuing Care
Barb Desilva	VP, Care Management

6. Safety Risks

This project presents no more than minimal risk to patients who participate in the STAR program. The deployment of the STAR program at participating sites utilizes care components that are already leveraged in Atrium Health facilities. While based on evidence and present in some facilities, these elements of care are not consistently applied across sites and infected patients.

There is always the risk of disclosure of a patient's private health information (PHI) or medical information. However, the processes identified in this protocol to enable the execution of this project, do not increase inherent risk of disclosure. Atrium Health utilizes several hard and soft safety controls in the protection of patient information and medical records. Security controls include, but are not limited to, multiple system firewalls, access restrictions to patient records and information, locked offices and buildings housing research and patient data, and multiple layers of username and password protected computer and system access. The project team will ensure that appropriate handling of patient PHI follows standard CHS procedure. In the event of PHI disclosure, the appropriate departments will be informed per legislation and privacy regulations.

6.1 Data and Safety Monitoring Plan

The Co-PIs are responsible for the ethical and compliant conduct of this project in accordance with local, state, and federal laws and regulations. Ongoing supervision of the study progress and conduct will be facilitated through at least monthly reports and quarterly meetings with key stakeholders and the PIs. These reports and meetings will address data updates, milestones, and concerns. Because this project presents no more than minimal risk to patients, per the FDA Guidance for Clinical Sponsors: Establishment and Operations of Clinical Trial Data Monitoring Committees, this study does not require oversight by a Data and Safety Monitoring Board or Committee.

7. Study Completion and Timeline

6.1 Completion

The study will be considered complete upon the determination of the Investigator and study team. Upon completion, a final report will be presented to detail all study findings, including primary and secondary outcomes.

6.2 Termination

The study will be terminated if the risk-benefit ratio becomes unacceptable owing to, for example, results of parallel studies or if the study conduct (e.g. data quality, protocol compliance) does not suggest a positive contribution toward the study objectives.

The Investigator has the right to close the study at any time. Closure will only occur after consultation with the executive committee.

6.3 Timeline

IMPACT Sepsis Project Timeline	Year 1											
	Mo1	Mo2	Mo3	Mo4	Mo5	Mo6	Mo7	Mo8	Mo9	Mo10	Mo11	Mo12
Protocol Development												
Patient Enrollment												
Statistical Analysis and Reporting												
Final Report												
Manuscript Development												

8. Retention of Records

Essential protocol documentation, including all IRB correspondence, will be retained for at least 5 years after the investigation is completed and all planned publications have been submitted. Documentation will be readily available upon request.

9. Ethical and Legal Issues

8.1 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with the applicable local laws and regulation(s).

Documented approval from appropriate agencies (e.g. IRB) will be obtained before the start of the study, according to GCP, local laws, regulations, and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented without consulting the IRB, as applicable. The Primary Investigators must assure that all study personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Investigator will be responsible for assuring that all the required data will be collected and properly documented.

8.2 Confidentiality

The evaluation component of this study will not involve direct contact with study subjects.

Patient confidentiality will be maintained by the Investigator, the Investigator's associates and co-workers. Confidentiality will be maintained according to ICH E6; 4.8.10, part O: "Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study trial are published, the patient's identity will remain confidential."

8.3 Disclosure of Data

The Investigator, his or her associates and co-workers, and the appropriate regulatory agencies may use the information and data included in this protocol as necessary for the conduct of the study. Information contained in this study, and data and results from the study are confidential and may not be disclosed without the written permission of the Investigator.

10. Publication Policy

Manuscript(s) and abstract(s) prepared from the data collected during this study will be prepared by the Principal and Sub-Investigators. The Principal Investigators or designee must send any draft manuscript, abstract, or conference presentation to members of the project Executive Committee for feedback and transparency, prior to submission of the final version. The Principal Investigators will be responsible for all relevant aspects regarding data reporting and publication.

The Principal Investigators or designee will ensure that the information and results regarding the study will be made publicly available on the internet at www.clinicaltrials.gov.

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