Study Protocol for:
Comparative Effectiveness of Readmission Reduction Interventions for Individuals With Sepsis or Pneumonia

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List of Common Abbreviations in Protocol:

RPM: Remote Patient Monitoring
SNF: Skilled Nursing Facility
RAR: Response Adaptive Randomization
CER: Comparative Effectiveness Research
STS: Structured Telephone Support

Research Synopsis

Study Population: Adults hospitalized for sepsis or lower respiratory tract infection age 21 and older with medium to high risk of readmission.

Design: A comparative effectiveness study using individual-level response adaptive randomization design along with a pragmatic, mixed-methods approach to compare combinations of five remote patient monitoring (RPM) strategies. Quantitative (e.g. self-report, electronic health record, process) and qualitative (e.g., interviews) data will be collected across multiple time points during the study period.

Sample Size: We expect to enroll 1,281 individuals.

Study Duration: The contract period begins August 3, 2020 and concludes August 31, 2026.

Background

Readmissions after sepsis or pneumonia exact an enormous toll on the health and quality of life of individuals and pose significant challenges for the health care system. Approximately one in five Medicare beneficiaries discharged from the hospital are readmitted within 30 days and a third in 90 days,[1] and older adults with multimorbidity are at higher risk.[2] Returning to the hospital after an index admission is shown to worsen patients' quality of life and increase their risk of healthcare-acquired infections,[3] despite the fact that many of these readmissions are avoidable.[4]

Individuals hospitalized for sepsis or pneumonia are particularly at risk for readmission and poor health outcomes. Among 14 million readmissions in the National Readmissions Database, sepsis and pneumonia (~3 million cases annually in US) were leading causes of readmissions.[5] Readmissions following sepsis and pneumonia are more common and associated with higher costs than readmissions due to heart failure, chronic obstructive lung disease (COPD), or myocardial infarction.[1,5-9] Survivors of both conditions experience reduced quality of life, increased mortality and morbidity,[10-12] and cognitive impairment and functional limitations.[13-15] Despite readmissions, one in three patients do not survive the year following sepsis or pneumonia, and those who do survive often experience persistent health deficits.[6-8,10,16] In a subset of hospitals owned by UPMC, a large integrated delivery and finance system in Pennsylvania, all-cause 30-day readmission rates for individuals with sepsis or pneumonia (23%) exceed the overall average (12%).

Further, readmissions following sepsis or pneumonia are often preventable. Up to nearly half of readmissions after sepsis can be attributed to preventable causes[17] and the preventability of readmission after pneumonia is recognized by the Centers for Medicare and Medicaid Services' (CMS) Hospital Readmission Reduction Program as an indicator of quality of care.[18] Most patients hospitalized with sepsis or pneumonia are >65 years of age and have multimorbidity.[19,20] Two-thirds of readmissions following sepsis or pneumonia were due to infection (~40%) and cardiovascular (15%) and respiratory disease (10%).[21] In theory, adequately monitoring patients, detecting early signs of deterioration, and triaging them to appropriate care would decrease unnecessary care utilization and increase patient stability. This is the premise of several widespread interventions such as in-hospital rapid response teams, post-discharge remote patient monitoring (RPM) for heart failure, and primary care-led monitoring in the community.[22,23]

However, there are critical gaps in knowledge regarding how comprehensively we should remotely monitor patient symptoms and types of health care teams best suited for responding to alerts to maximize patient time at home. The standard of care for patients with multimorbidity is to provide some level of care coordination or care provision after discharge, as we know it works. There is a large body of evidence demonstrating that post-acute care models as a whole reduce the risk of an individual returning to the hospital after discharge.[24] Among these, more complex interventions that leverage multiple components and multiple care providers have greater effect on maintaining patients at home longer after discharge.[24] Specific successful model components include care coordination/care management activities and patient self-management education.[25,26]

A key priority for the health care system is understanding how to effectively deploy the post-acute workforce in the community.[27,28] Structured Telephone Support (STS), or telephonically connecting with patients post-discharge to assess health status, reconcile medications, and provide patient education, is a well-studied, effective strategy. Within UPMC, deployment of STS for several years across a wide population has successfully reduced readmissions. However, STS may be insufficient for patients at higher risk of readmission.[29] For more complex patients, RPM platforms have extended the reach of

providers by regularly collecting patient-reported data on vital signs and symptoms, allowing early recognition of worsening disease and deploying interventions promptly.[30] Provider monitoring of symptom exacerbation is important because patients alone are unreliable in reporting worsening symptoms.[26,31] RPM platforms have received FDA approval, reduced readmissions in multiple observational and randomized controlled studies, and are routinely used in clinical care.[26,32] While patient acceptability of RPM is high, RPM platforms typically monitor one disease or condition (e.g., heart failure exacerbation in patients hospitalized for heart failure). Given that multimorbidity is associated with hospitalization for serious infection and readmissions are often due to worsening of underlying chronic conditions, utilizing RPM to assess multiple disease states could be more successful in early identification and intervention. However, the optimal post-acute care strategy for patients with multimorbidity is unknown.

Additionally, more information about the spectrum of services delivered within and alongside RPM is critical to effectively meeting patients' needs. There is conflicting evidence about whether models that couple RPM with an alert-triggered provider response (Standard Team) or a more intensive patient engagement model (Enhanced Team) are more effective,[33-35] the reason for which may be that studies often fail to define specific intervention components.[36] Several studies show that multidisciplinary teams that periodically conduct in-person or virtual home visits and specialize in chronic disease management, care coordination, and patient education about self-management may increase time spent at home.[37,38] However, this approach is resource intense and may be difficult to scale across large geographic areas.[39] Noting that RPM findings are often confounded by additional in-home care received by both intervention and control groups, one study measured the effect of RPM versus usual outpatient care in a sample of patients not receiving concurrent home-based care and showed decreased emergency department (ED) utilization and hospital length of stay and increased quality of life among the group receiving RPM.[40] The study of RPM without explicit investigation of the model of care into which RPM is built is a critical gap in the comparative effectiveness literature.[41]

Significance

UPMC's integrated delivery and finance system offers a unique environment for conducting a patient-centered comparative effectiveness research (CER) study that will rapidly increase the ability of patients, caregivers, and other stakeholders to make informed decisions about post-acute care after sepsis or pneumonia.[30] Building upon years of collaborative work involving care models for individuals with multimorbidity, stakeholder engagement, pilot testing, and existing research, this study will provide much-needed information about how best to support individuals in their homes after discharge.

UPMC's existing technology infrastructure is well-suited to support the proposed work. Our RPM platform allows for synchronous and asynchronous communication between patients and providers using a variety of devices including patient-owned smart phones, tablets, and computers to monitor symptom exacerbations and avoid the potentially preventable ED visits and hospitalizations.[42] This technology, which is currently used to engage with and monitor patients via modules that target individuals with conditions such as COPD, heart failure, cancer, infectious disease, and frailty, can easily be adapted for study purposes. Currently, over 500 hospitals have contracts for using this same technology to provide services for improving the health of a variety of patient populations. In addition, care management databases, smart phone applications, and mobile health products developed through the UPMC Insurance Services Division (ISD) Consumer Innovation Department are all designed to expand our ability to provide, more efficiently, comprehensive services to some of our most vulnerable patients.

RPM supports multiple care models within UPMC. The standard of care when using RPM is to code patient-reported data into alert levels (low, medium, high). Medium and high alerts are sent to a nurse-led call center, where staff contact the member or provider and recommend appropriate action such as scheduling a follow-up appointment or visiting the ED. RPM is also used to support an enhanced care team led by a certified registered nurse practitioner (CRNP) with prescribing authority. This team delivers home-based or virtual care management, which includes advanced care planning and goals of care discussions and triages and manages symptoms reported via RPM. Internal evaluation data show that members touched by this team have reduced unplanned care and increased days at home.

From a technological standpoint, the use of telemedicine, including RPM, is rapidly expanding across the US. Several recently released industry reports predict high growth in telemedicine reimbursement and system investments.[43-45] Medicare reimbursement policies are quickly evolving to support models of care that use remote monitoring to manage chronic conditions.[46] Major insurers across the U.S. offer RPM and all have telehealth reimbursement policies, with varying conditions about where it needs to be delivered.[47,48] Nearly 1800 hospitals across the US currently use apps to support RPM[49] and 2 in 3 providers plan to use RPM in the future.[50] Finally, RPM is the standard of care for several chronic conditions.[51]

Nurse practitioners (NPs) already play a major role in providing telemedicine care in the US. In an analysis of the Minnesota All Payer Claims Database nearly half (46%) of all 2015 telemedicine visits were delivered by NPs.[52] Multidisciplinary palliative care teams that include NPs are used throughout the US health care system,[47,53] and 67% of US hospitals with 50+ beds have palliative care teams, an increase from 53% in 2008.[54] Among providers conducting home-based care, NPs form the largest provider group and provide care across the largest geographic area.[55]

Training for NPs in advanced illness care using telemedicine is scalable. NPs can obtain academic certificates in palliative care through accredited higher education institutions (generally averaging 150 hours of study[56,57]) and through in-person or web-based courses and trainings offered through various organizations, such as Vital Talk[58] and Defining Hope.[59] Thus, if palliative care NP-led programs are effective, this program can be generalized to other healthcare systems. As noted by Lazur et al., the rapid increase in use of telehealth technology "has outpaced the release of research about this model of care."[60] This research is optimally timed to provide relevant research that health systems can leverage as they implement telehealth technology to support critically ill populations.

Our research will help to efficiently and effectively answer questions that are critical to patients, caregivers, providers, and payers regarding how to ensure individuals remain in their homes after discharge. Studies consistently show that patients prefer to maximize the time spent at home instead of a healthcare facility, especially during the last six months of life.[27,61-63] Stakeholder feedback during the study design process clearly articulated a need to increase the efficiency of traditional research, ensuring that the health care system has access to quality evidence to learn quickly what works best for whom. Therefore, we propose to use an adaptive platform trial, which uses a common platform to enroll all patients with the condition of interest (e.g., sepsis or pneumonia) and tests multiple interventions simultaneously.[64,65] The adaptive design incorporates rules to modify treatment arm randomization ratios over time by updating our Bayesian statistical model as new patients are accrued and preferentially enrolling to arms for which evidence of benefit is the strongest. This approach requires a smaller sample size (and potentially shorter study timelines) compared to a traditional trial and reduces the likelihood of exposing patients to therapies that are ineffective or harmful. The rules to change randomization probabilities to individual arms are written prior to start of the trial. The I-SPY 2[66] trial is the best known example of an adaptive platform trial and this design is also being used for other

conditions, including glioblastoma multiforme,[67] pancreatic cancer,[68] Parkinson's disease,[69] and cystic fibrosis.[70] Therefore, we propose to test multiple combinations of RPM and care team interventions to determine if any of them are superior to STS (**Aim 1**).

Ensuring that the most resource-intensive interventions are directed toward patients most likely to benefit is a critical challenge for the health care system as it strives to care for increasingly complex populations with limited resources.[28,71,72] Although precision medicine has traditionally focused on biomarkers (e.g., genomic markers), we will focus on patient-level clinical, social, and environmental factors to tailor service delivery (precision population health) to patients who are most likely to benefit (**Aim 2**). In addition to conducting traditional exploratory subgroup analyses testing one variable (or risk prediction score) at a time using a regression-based approach, we propose a novel machine learning-based algorithm for several reasons. First, we can model many factors simultaneously, leaving the door open for complex interactions to emerge from the data in a flexible manner. Second, the machine-learning models (e.g., causal forest) do not require assumptions regarding the relationship between a covariate and treatment effectiveness. Third, we can predict treatment effectiveness at the patient-level, allowing us to develop personalized strategies.

Objectives

This goal of this study is to answer critical questions about how to best design RPM programs to maximize home-days and minimize readmissions for patients discharged after sepsis or lower respiratory tract infection. Moreover, this study seeks to provide valuable information about how RPM programs may benefit patients discharged after other diseases. This information will be beneficial to patients, providers, payers, health systems, and community organizations seeking to maximize days spent at home.

Aims

There is uncertainty regarding how comprehensively we should remotely monitor patient symptoms and which health care team is best suited to triage care in the post-acute setting. While STS is an effective strategy, telemedicine-based care models might be a better option for patients at higher risk of readmission. These models allow at-home surveillance using a RPM platform, early detection of worsening of health, and deployment of an intervention once an alert is generated. RPM is typically used to monitor and prevent readmissions for a single disease (e.g., heart failure). This low-intensity RPM (**RPM-Low**) approach may not be effective in patients discharged after sepsis and pneumonia where readmissions are frequently due to worsening of sub-clinical disease, and surveillance for multiple conditions (**RPM-High**) may be necessary. An important element of RPM is deploying interventions once an alert has been received. Typically, a physician or a nurse responds to alerts (**Standard Team**), but dedicated nurse-practitioner (NP)-led multidisciplinary teams may be more effective (**Enhanced Team**).

We will randomize patients to five arms: 1. STS; 2. single-condition RPM with standard provider-led responses to alerts (RPM-Low + Standard Team); 3. single-condition RPM with NP-led multidisciplinary team patient engagement (RPM-Low + Enhanced Team); 4. multi-condition RPM with standard provider-led responses to alerts (RPM-High + Standard Team); and, 5. multi-condition RPM with NP-led multidisciplinary team patient engagement (RPM-High + Enhanced Team). The RPM care models tested in this study may not be more effective than STS or more than one care model may be effective in the broad group of patients. In either scenario, identifying subgroups for whom these care models are most effective is consistent with "precision population health," which targets interventions based on clinical, social, and environmental determinants of disease.

Aim 1: To compare the effectiveness of care models that vary based on intensity of RPM and team composition to increase the number of days spent at home among patients discharged home after sepsis or pneumonia.

Aim 1a. To determine if patients randomized to RPM-Low + Standard Team, RPM-Low + Enhanced Team, RPM-High + Standard Team, and RPM-High + Enhanced Team interventions have higher home days compared to STS.

Aim 1b. To determine the optimal care model (listed in Aim 1a) in terms of the number of days spent at home.

Aim 2: To determine the patient subgroups for whom individual RPM care models are most effective.

Aim 3: To understand contextual factors related to intervention adoption, satisfaction, effectiveness, and sustainability.

Aim 3a. To understand patients' and intervention providers' perceptions of contributors to intervention acceptability, value, and satisfaction.

Aim 3b. To determine in what ways the interventions impact the primary outcomes of post-discharge home days as well as secondary outcomes, including functional status and quality of life.

Aim 3c. To assess facilitators and barriers to intervention acceptability, feasibility, fidelity and sustainability.

Aim 3d. To explore considerations and strategies that can be used to support scaling of the interventions for other patient populations and health care settings.

Interventions

All intervention components are currently in use by patients with complex care needs and were originally designed to address ongoing care access issues while not compromising the core, evidence-based components of each intervention. The technology components of these interventions will be delivered through and/or supported by UPMC's existing RPM platform, which can enhance symptom monitoring and improve consistency of patient and provider contact.[73] Each intervention is designed to facilitate symptom monitoring, identification of worsening disease, and adherence to follow up care recommendations. RPM interventions will start when the participant returns home, regardless of whether they had a temporary SNF stay between hospital and home or not. Participants will only answer RPM questions while at home. Moreover, the interventions are designed to proactively address these issues through actions of the care teams. Participants and physicians are free to discontinue RPM programs per existing programmatic and clinical protocols if doing so is in the best interest of the patient. Study comparators (1. STS, 2. RPM-Low + Standard Team, 3. RPM-Low + Enhanced Team, 4. RPM-High + Standard Team, and 5. RPM-High + Enhanced Team) are a combination of the evidence-based components described below:

- Structured Telephone Support (STS):[29] Structured telephone support (STS) consists of post-discharge assessment, education, and medication reconciliation delivered telephonically by a health plan case manager, home care as needed, and follow-up with the primary care within seven days post-discharge.
- Low-intensity Remote Patient Monitoring (RPM-Low):[74] Questions are pushed to members multiple times per week for up to 90 days post-discharge. Questions are limited to those checking vital signs that indicate worsening of infection. Patient answers to RPM questions trigger High or Medium alerts, which trigger a response by members of the intervention care team (see below).

- High-intensity Remote Patient Monitoring (RPM-High):[22] Questions are pushed to members multiple times per week for up to 90 days post-discharge. Questions include monitoring vital signs for worsening infection but also ask about factors that would indicate worsening of underlying heart or lung conditions, such as weight gain or shortness of breath. Patient answers to RPM questions trigger High or Medium alerts, which trigger a response by members of the intervention care team.
- Standard Team:[40,75] RPM alerts are screened by a nurse-staffed call center. Nurses determine whether emergency care is needed. If not, nurses contact the patient and/or the patients' PCP or specialist to coordinate care and ensure timely follow-up.
- Enhanced Team:[25,37,76] RPM alerts are screened by a nurse-staffed call center. Nurses determine whether emergency care is needed. If not, the call center alerts a multidisciplinary care team that is led by a certified registered nurse practitioner (CRNP). CRNPs, who operate in a palliative care role, have prescribing authority and can modify care plans. In addition to reacting to RPM triggers, team members (e.g., CRNP, social workers, nurses) meet with the patient in-person or virtually in the week after discharge and at least twice more in the next 90 days, conduct assessments and a pharmacy review, develop care plans, and complete a POLST (physician orders for life-sustaining treatment) or a PA Advance Directive.

RPM pathway questions

	Category	Question	Audience	Frequency
1	Thermometer	Based on the thermometer, how are you currently feeling (0-10)? 0, 1, 2: **SKIP ALL SYMPTOM QUESTIONS** 3, 4, 5, 6: **ASK ALL APPLICABLE SYMPTOM QUESTIONS** 7-10 *(HIGH ALERT)* **ASK ALL APPLICABLE SYMPTOM QUESTIONS**	All	Twice per week
2	Symptom	Have you had swelling in your legs and ankles in the past 3 days? Yes *(MEDIUM ALERT)* No	RPM High only	Twice per week
3	Symptom	Have you had a worsening cough or chest pain in the past three days? Yes *(MEDIUM ALERT)* No	RPM High only	Twice per week
4	Symptom	Are you having pain? Yes No **If yes**: Is your pain worse than usual? Yes *(MEDIUM ALERT)* No Pain Health Tip	All	Twice per week
5	Symptom	Are you having problems breathing? Yes No **If yes**: Is your breathing worse than usual? Yes *(MEDIUM ALERT)* No Shortness of Breath Health Tip	All	Twice per week
6	Symptom	Do you have nausea or vomiting? Yes No **If yes:** Are you unable to eat or drink because nausea and/or vomiting? Yes *(MEDIUM ALERT)* No	All	Twice per week
7	Symptom	Do you have problems moving your bowels? Yes No **If yes:** Has it been more than 3 days since you had a bowel movement or is your stool hard to pass? Yes *(MEDIUM ALERT)* No	All	Twice per week
8	Symptom	Do you feel lightheaded or faint? Yes *(MEDIUM ALERT)* No	All	Twice per week
9	Symptom	Have you fallen in the past week? Yes *(MEDIUM ALERT)* No	All	Weekly

10	Symptom	Do you have fever or chills? Yes *(MEDIUM ALERT)* No	All	Twice per week
11	Symptom	Do you feel like you must go to your doctor's office or emergency room in the next few days? Yes *(MEDIUM ALERT)* No	All	Twice per week
12	Medication	Do you have questions about your medicines or medical conditions? Yes *(MEDIUM ALERT)* No	All	Twice per week
13	Medication	Have you missed any doses of your antibiotic in the past three days? Yes *(MEDIUM ALERT)* No	All	Twice per week
14	Medication	Have you started a new medicine in the last month? Yes *(MEDIUM ALERT)* No	All	Monthly
15	Help	Do you have someone who can help you with transportation bill paying and shopping? Yes No *(MEDIUM ALERT)*	RPM High Enhanced RPM Low Enhanced	Monthly
16	Help	Do you have problems caring for yourself at home? Yes *(MEDIUM ALERT)* No	RPM High Enhanced RPM Low Enhanced	Monthly
17	PHQ	PHQ 2/9		Monthly
18	FAMCARE	FAMCARE P13		Monthly
	Video	Video about advanced care planning		One time
	Video	Video about choosing a health agent		One time

Study Design/Methodology

We have chosen an individual-level response adaptive randomized platform study design along with a pragmatic, mixed-methods approach to compare five RPM program configurations for delivering post-acute monitoring to patients with sepsis or lower respiratory tract infection across western and central Pennsylvania.

Study Setting

Participants will be recruited from the hospitals listed below. All hospitals are located in Pennsylvania. Historical data suggests that recruiting from these hospitals will allow us to reach our target sample size. For detailed recruitment methods, please refer to the Recruitment Plan

Recruitment Sites		
Armstrong County Memorial Hospital	UPMC Hamot	UPMC Northwest
Meadville Medical Center	UPMC Horizon	UPMC Passavant
Conemaugh Memorial Medical Center	UPMC Jameson	UPMC Presbyterian
St. Clair Hospital	UPMC Magee Women's Hospital	UPMC Shadyside
UPMC Altoona	UPMC McKeesport	UPMC St. Margaret
UPMC East	UPMC Mercy	Washington Hospital
Heritage Valley Beaver	Heritage Valley Sewickley	

Randomization Procedure

The study will use web-based randomization to one of the five care models for those individuals who consent to participate in the study. Once a research coordinator determines eligibility, obtains informed consent, and the patient is discharged to home while maintaining eligibility, he or she will enter in key identification information, and the system will then generate a Study ID (numeric identification number) along with assignment to an intervention arm. Randomization will initially be fixed with 30% of patients randomized to STS and the remaining 70% of patients randomized 1:1:1:1 between the four RPM care models. After 250 patients have been randomized and followed for 90 days, the first interim analyses will be conducted and RAR will begin and continue to be updated every three months. During the RAR phase, the randomization to STS will remain fixed to be 30% of patients and the remaining 70% of patients will be randomized to one of the four RPM models preferentially based on the probability that each RPM care model is optimal.

While the research coordinators will see each assigned intervention arm per the randomization process, they will be blinded to overall changes in treatment allocation rates. Other study team members, including Principal Investigators, Co-Investigators, statistical analysts, and database administrators will also be blinded to treatment allocation rates during the course of data collection.

Study Population

Our study population will consist of patients who are UPMC Health Plan members or have Medicare Fee-for-Service insurance age 21 and older hospitalized with a primary diagnosis of sepsis or lower respiratory tract infection, who are discharged to home (from the hospital or after a SNF stay of 28 days or fewer), and are at moderate- or high-risk for readmission.

Inclusion/Exclusion Criteria

1. Inclusion criteria
    a. UPMC Health Plan member or patient with Medicare Fee-for-Service insurance
    b. Treated at a prespecified hospital for sepsis or lower respiratory tract infection
    c. Age 21 or older
    d. Medium or high risk of readmission
2. Exclusion criteria
    a. Admitted from setting other than home, independent living, or personal care home
    b. Receiving hospice at time of admission
    c. For Health Plan members: being discharged on/to hospice, Inpatient Rehabilitation, long-term acute care hospital, or assisted living facility
    d. For Medicare Fee-for-Service enrollees: being discharged on/to hospice, Inpatient Rehabilitation, long-term acute care hospital, skilled nursing facility, or assisted living facility
    e. Currently participating in UPMC Advanced Illness Care program
    f. Unable to participate in RPM due to lack of technology/internet connection
    g. Known Pregnancy
    h. Severe, persistent cognitive impairment
    i. PCP disapproves of patient being in remote patient monitoring program
    j. No PCP available to participate
    k. Patients who are discharged from hospital to skilled nursing facility and stay at the skilled nursing facility for greater than 28 days

Unanticipated Enrollment in UPMC Advanced Illness Care Program

The UPMC Advanced Illness Care (AIC) Program is a 6-month palliative care program offered by UPMC Health Plan to members in need of palliative care. Referrals to this program are made both at hospital discharge and during the course of routine outpatient care.

It is rare but possible for a randomized ACCOMPLISH participant to be enrolled into the UPMC Advanced Illness Care (AIC) Program. The Co-Enrollment Workflow is a detailed process designed to prevent this issue; however, co-enrollments are still possible due to organizational complexity and care process variation.

In the event that a randomized ACCOMPLISH participant is also enrolled in the AIC program, the study team will follow a strict intent to treat study design and continue to collect outcomes data per the established timelines and processes. If the number of randomized participants is greater than 10 at the end of all recruitment and data collection, a sensitivity analysis will be performed to determine if the AIC participants have significantly different outcomes than the participants enrolled in the study as planned.

Potentially Eligible Patient Dashboard Identification and Chart Review Process:

Potential participants are initially identified through a dashboard populated daily with inpatient data pulled from an UPMC's electronic health record system. This dashboard shows the medical record number of inpatients who meet some ACCOMPLISH study inclusion criteria such as hospital, age, insurance type, readmission risk score (derived from a predictive model), and pre-specified diagnostic indicators suggestive of sepsis and lower respiratory tract infection (antibiotics ordered for at least two days and at least one culture ordered within the first three days of a hospital stay). The RCs examine the medical records of patients identified on the dashboard for further eligibility criteria including where a patient was admitted from, their planned discharge location (home, SNF, hospice, etc), pregnancy

status, and specific diagnostic indicators of sepsis or lower respiratory tract infection. The table below shows standard criteria found in medical records to use as a guideline determine if an RC can independently deem the patient clinically eligible for the study, or if a clinically-trained PI/Co-I needs to review the patient's chart to confirm clinical eligibility.

Condition	Criteria used by research coordinator
Lower respiratory tract infection	**All three criteria were met:** • Received at least two days of antibiotics, which were started within 24 hours of hospital presentation • At least one culture from blood or lower respiratory tract ordered within first three days of hospital presentation • Pneumonia or chronic obstructive pulmonary disease (COPD) exacerbation considered as a potential diagnosis
Sepsis	**All three criteria were met:** • Clear source of infection (e.g., urinary tract infection, catheter-related blood stream infection, abscess) OR at least one culture (e.g., blood, urine, lower respiratory tract) ordered within the first three days • Received at least two days of antibiotics, which were started within 24 hours of hospital presentation • At least one criterion for organ dysfunction or notes mentioned "sepsis" or "septic shock": o Elevated serum creatinine and blood urea nitrogen levels (kidney function) o Elevated serum lactate levels o Received vasopressors (e.g., dobutamine, norepinephrine, epinephrine)
COVID-19	**All three criteria were met:** • COVID-19 was the primary reason for hospital admission • Presence of respiratory symptoms (e.g., shortness of breath, cough dyspnea) • Prescribed/ordered one of the following during hospitalization: o Dexamethasone (6 mg daily) o One of the following: Remdesivir, Sotrovimab, Bebtelovimab, Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use), Tocilizumab, Baricitinib o Received vasopressors, high-flow oxygen, invasive or non-invasive mechanical ventilation

Measures

Primary outcome

Post-discharge home days at 90 days: Home days will be calculated as days alive and at home, a composite of mortality and morbidity. We included mortality to ensure that competing risk of death will not affect this outcome. The proposed interventions are likely to have a small effect on time to death in these patients.

Secondary outcomes

Functional Status: will be measured at baseline and 90 days, using the PROMIS Physical Function – for Mobility Aid Users-SF. The Patient-Reported Outcomes Measurement Information System (PROMIS™) provides item banks that offer the potential for PRO measurement that is efficient (minimizes item number without compromising reliability) flexible (enables optional use of interchangeable items), and precise (has minimal error in estimate) measurement of commonly-studied PROs.[77] PROMIS item banks and their short forms provide evidence they are reliable and precise measures of generic symptoms and functional reports comparable to legacy instruments.[78]

Health-related Quality of Life: will be measured at baseline and 90 days, using the Quality of Life Enjoyment and Satisfaction Questionnaire-SF. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a self-report measure designed to enable investigators to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning.[79]

Transition to Hospice: will be assessed via claims data at 90 days to see if member transitioned to hospice care during the course of the study.

Emergent outpatient utilization: will be assessed via claims data at 90 days for a count of urgent outpatient visits for study participants.

Readmissions: will be assessed via claims data at day 7, 30, and 90 for any inpatient admissions after index admission, and whether readmission hospital was the same as index hospital.

Mortality: will be assessed via claims data at 90 days to see if and when the member/participant passes away.

Covariates

We will include variables likely to influence the strength of the relationship between the interventions and outcomes and included variables within domains (patient-level, socioecological, and care delivery and utilization) that have hypothesized associations with the primary and secondary outcomes. These covariates will be the basis for Aim 2 analyses. Finally, we will monitor adherence to pre-established intervention workflows and RPM response rates throughout the study to ensure that intervention fidelity is maintained and can be accounted for in the analyses.

Domain: Patient-Level:

> *Patient Demographics and clinical characteristics:* We include in our baseline survey questions regarding age, race, ethnicity, marital status, and gender. Insurance type and the Charleston Comorbidity index will be pulled from administrative and claims data at baseline. We will ask questions about generalized anxiety disorder, depressed mood and anhedonia, health literacy, and comfort with technology.

Living at home status: We include in our baseline and 90-day survey questions regarding whether a participant lives at home alone or with others. If participants live with others, an additional question to identify their living companion(s) is asked. The participant can identify multiple living companions from a list.

Payer: Based on literature review and the experience of our study investigators, we do not expect large differences in the distributions of post-discharge home days between UPMC Health Plan and MC FFS study participants. However, in the event that participant payer (UPMC Health Plan or MC FFS) is predictive of home day distribution, randomization of study interventions ensures that effectiveness comparisons are guaranteed to remain unbiased toward any particular arm. Thus, our primary analysis model will remain as it is currently stated in the Statistical Analysis Plan.

To maximize oversight the proposed new subgroup (MC FFS), home days distributions of each payer type group will be reported to the DSMB in regular quarterly interim analysis reports.

In addition, we will conduct two types of sensitivity analyses to detect any differences in the two distributions after data collection:

1. We will fit two additional proportional logit models accounting for payer type:
    a. One logit model including a term for payer which will capture proportional shifts in home days across payer groups; and
    b. A second model that will include different intercept terms for the payer type groups. This model will capture non-proportional shifts in home days across both groups.
2. We will explore potential differential effects of RPM care models across payer types. One model will estimate interaction terms between RPM arm and payer type; and another will fit separate proportional logit models to UPMC Health Plan and MC FFS participants.

Domain: Socioecological:

Distance to primary care provider (PCP) office: Distance from participant's home address to the PCP office in miles will be pulled from administrative data at baseline.

Area Deprivation Index (ADI): The ADI will be a composite score of socioeconomic variables to indicate neighborhood socioeconomic status pulled from administrative data at baseline.

Domain: Care Delivery and Utilization:

Non-urgent outpatient care utilization: The count of non-urgent outpatient visits that occur per participant during the observation period (primary and specialty care visits) will be pulled from claims data at 90 days.

Prior admissions: The number of inpatient admissions in 90 days prior to index admission will be pulled at baseline from claims data.

ICU stay, mechanical ventilation, inpatient dialysis: Whether participant received each type of care during index hospitalization and if so, for how many days will be pulled at baseline from the electronic health record and claims data.

Skilled nursing facility stay: Whether a patient had a post-index hospitalization stay in a SNF for 28 days or fewer before being discharged home.

Index hospital: The location of the index hospitalization, hospital bed size, and hospital teaching status will be pulled from claims data at baseline.

A summary of measures is shown below:

STUDY VARIABLES	DATA SOURCE	WHEN MEASURED	HOW MEASURED
Primary Outcome			
Post-discharge home days	Claims data, EHR data, Health Information Exchange (HIE) data, Participant	90 days	Total number of days alive and out of acute care hospitals, inpatient rehabilitation, or skilled nursing facilities[80,81]
Secondary Outcomes			
Functional status	Participant	Baseline, 90 days	PROMIS Physical Function – for Mobility Aid Users[77,78]
Health-related Quality of Life	Participant	Baseline, 90 days	Quality of Life Enjoyment and Satisfaction Questionnaire-SF (QLESQ-SF)[79]
Transition to Hospice	Claims data	90 days	Whether member transitioned to hospice care
Emergent outpatient utilization	Claims data, EHR data, HIE data, Participant	90 days	Count of urgent outpatient visits (ED visits & urgent care visits)
Readmissions	Claims data, EHR data, HIE data, Participant	7, 30, and 90 days	Subsequent inpatient admission after index admission, and whether readmission hospital was same as index hospital[82]
Mortality	Claims data, EHR data	90 days	Whether member dies during observation period
Covariates			
Domain: Patient-Level			
Patient demographics & clinical characteristics	Administrative & claims data	Baseline	Age, race, gender, insurance type, Charlson Comorbidity Index[20,83]
Living at home status	Participant	Baseline	Whether participant lives alone or with others
Payer	EHR data	Baseline	Whether participant is insured by UPMC Health Plan or Medicare Fee-for-Service
Domain: Socioecological			
Distance to primary care provider (PCP) office	Administrative data	Baseline	Distance from participant's home address to PCP office (miles)
Area Deprivation Index (ADI)	Administrative data	Baseline	Composite score of socioeconomic variables to indicate neighborhood SES[84]
Domain: Care Delivery & Utilization			
Non-urgent outpatient care utilization	Claims data, EHR data, Participant	90 days	Count of non-urgent outpatient visits that occur during the observation period (primary and specialty care visits)
Prior admissions	Claims data, EHR data	Baseline	Number of inpatient admissions in 90 days prior to index admission
ICU stay, mechanical ventilation, inpatient dialysis	EHR/Claims data	Baseline	Whether participant received each type of care during index hospitalization and if so, for how many days

Skilled nursing facility stay	EHR/clinicians	Baseline	Whether the patient had a post-index hospitalization stay in a SNF for 28 days or fewer before being discharged home
Index hospital	EHR/Claims data	Baseline	Location of index hospitalization, hospital bed size, and teaching status
Process			
Integrity of care/fidelity	Research staff, clinicians	90 days	Checklist for RM and care approaches/processes
RPM compliance	Research staff, clinicians	90 days	RPM response rates

Process measures

The study team will monitor adherence to pre-established intervention workflows and RPM response rates throughout the study to ensure that intervention fidelity is maintained and can be accounted for in the analyses.

Integrity of care/fidelity: The research staff in conjunction with the remote monitoring supervisors following the RPM usual workflow, have developed an Interrater Reliability checklist to monitor fidelity to RPM intervention protocols and processes. This check will be conducted by either supervisors or peers every quarter to ensure established processes are being followed.

Fidelity to the STS arm protocol will be ensured by the telephonic case manager supervisor's routine monitoring of post-discharge phone calls. The research team will receive quarterly reports documenting that each study participant randomized to the STS arm received the STS usual care activities in accordance with usual care.

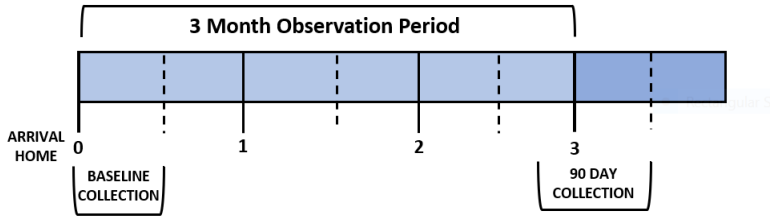
Participant RPM compliance: The research staff will review RPM response rate data at 90 days to characterize patient compliance to the RPM interventions.

> *No Response:* Participants who are enrolled in the RPM program, but do not begin the RPM program on their electronic device will be contacted by the RPM call center staff to address any technology issues or questions that have arisen during the first seven days of enrollment. If the patient still has not interacted with the RPM program after 14 days, the Research Team will attempt one final call to the participant to address issues. If the participant still does not participate after the call from the Research Team, the participant will remain able to join the program at any point during the 90-day post-discharge intervention period, but will no longer be contacted and encouraged to participate in the program by the research team or the RPM staff.
>
> *Non-Responder:* Patients who start the RPM program but fail to respond to RPM questions for 2 consecutive weeks are considered "non-responders". The remote monitoring call center staff will review non-responders' charts for hospital readmission, death, or admission to hospice. If the patient has not been readmitted, died, or went to hospice, they will be contacted by RPM staff to offer assistance and encouragement to respond. If there is still no participation after RPM staff outreach, the participant will continue to receive automated invitations to respond to pathways, but will no longer be encouraged to participate by the research team or RPM staff.

Study Duration/ Timeline

August 1, 2020 – December 31, 2020: Pre-Implementation Period
January 1, 2021 – October 31, 2024: Implementation Period
November 1, 2024 – July 31, 2026: Post-Implementation Period

Participants will be consented and enrolled in the hospital. Baseline surveys will be collected during participants' the first two weeks at home. The study observation period will be for 90 days post discharge to home (whether from hospital or SNF). Ninety-day surveys will be collected one week prior to and two weeks after the end of the observation period. This timeline is documented in the diagram below.



Data Collection

Quantitative data is collected from several sources. Self-report assessments are gathered at baseline and 90-days using REDCap Cloud, a secure data collection platform. Clinical data, additional patient demographic/descriptive information, and health care utilization data is extracted from electronic health records and payer claims at baseline and 90-days. For individuals who withdraw from the study, data will be retained up to the point of study withdrawal.

Qualitative telephone interviews are conducted to understand patient or caregiver intervention-related experiences. We will conduct interviews with 80 patients (spread approximately evenly across each of the 4 intervention arms). If a patient is unable to participate in an interview due to medical complexity, we attempt to interview his/her primary caregiver. All audio recordings of interviews are transcribed by experienced qualitative researchers and de-identified. We use a unique study ID to label all study materials related to participation with a tracking log as the only link to identifying information. Transcripts will be stored on a secure cloud-based environment approved by UPMC.

We use the NVivo 12 (QSR International, Australia) platform for data analysis. A constant comparative thematic content approach will be used to analyze the qualitative data. Our qualitative analysis is be iterative. A separate codebook is be developed for each interview type (i.e. patient, intervention providers, primary care physicians) with the input of the Co-Investigators and the Stakeholder Advisory Board. We assess inter-rater reliability using percent agreement and kappa scores. Upon acceptable interrater reliability, the qualitative research team thematically codes all qualitative documents.

Sample Size

The study planned to enroll 1,668 patients across the five different arms (STS, RPM-Low + Standard Team, RPM-Low + Enhanced Team, RPM-High + Standard Team, and RPM-High + Enhanced Team). From this sample 1168 patients were expected to be discharged directly to home and 500 patients were expected to be discharged to SNF and then home. Accounting for an estimated 10% attrition, the final analytic sample size was expected to be 1,500.
However, in November 2023 it was decided to reduce the sample size to 1,281 due to recruitment challenges.

Informed Consent Process

The informed consent process begins with a member of the hospital staff. The staff will ask pre-identified, potentially eligible patients if they are interested in learning more about a research study. If the patient is interested and agrees to learn more about the study, the hospital staff member will inform the Research Team members and outreach for consent will begin.

Electronic, verbal, or paper-based consent for the study will be obtained during a hospital admission at various UPMC and non-UPMC sites. Research Team members, who have completed institution-specific Human Research Protection Office (HRPO) CITI trainings, will assist the subject in navigating the consent process. The consent process will provide subjects with a clear explanation of the objectives, procedures, risks and benefits of the study and their rights as study participants. A Frequently Asked Questions (FAQ) page will also be available to the subjects. Members of the Research Team begin the consent process by reading through an IRB approved script explaining the study and conduct a cognitive screener. If the patient is interested and meets eligibility criteria, the Research Team can continue with obtaining consent. Written or verbal consent with a proxy may also be obtained through an IRB approved proxy consent process if the participant has an altered mental state (fails any of the screener) but still wishes to participant in the study.

Research Team members will be available in-person, over the phone, or via video to answer all questions related to the informed consent process and study procedures prior to the member consenting to participation. The FAQ sheet will be available to members to serve as a quick reference guide to the study. Consent for the qualitative interviews will also be obtained during this process.

Participants recruited from non-UPMC hospitals will be asked to sign a hospital-specific medical records release form after signing the informed consent form. In the unlikely event that a participant recruited from a non-UPMC hospital is randomized to a remote patient monitoring intervention arm and there is insufficient hospitalization clinical information available in the UPMC Health Plan's member portal, the signed release form will be provided to the remote patient monitoring call center so they can request the records needed to provide post-discharge remote patient monitoring care to the participant.

Participants will retain their right to have their questions answered by Principal or Co-Investigators or a member of the Research Team via telephone or through any other preferred method of communication. The Research Team believes that informed consent is an ongoing process in any study and so will continue to educate participants about the nature of the research and will address any questions that arise throughout the course of the study. These efforts will comply fully with the Health Insurance Portability and Accountability Act (HIPAA) and the informed consent guidelines of the University of Pittsburgh IRB.

Participants who have a SNF stay prior to going home will be reminded of their study enrollment by a UPMC care coordinator (if available) while preparing to go home.

Privacy and Confidentiality

Self-report and qualitative data collected for this study will be used for research purposes only. Access to the data will be restricted to the Co-Principal Investigators, Co-Investigators, and other Research Team members. Research staff will sign confidentiality agreements as required. Identifying links to all data will be maintained at baseline and other data collection time points using a secure password-protected server, accessible only by authorized members of the study team. Once the data is collected, the file containing the link between identifying information and the participant's data will be destroyed at the earliest timepoint possible.

Qualitative data will be audio recorded using digital recording devices, transferred to a secure server immediately following recording and deleted as soon as it is fully transcribed. Interviews will be audio recorded, transcribed, and scrubbed of identifying information. Participants will be asked not to include any identifying information in their responses, and coders will not code any identifying information that may be provided inadvertently.

All data obtained over the course of the study will be confidential and secure. Paper study records will be secured using the “double-lock” method (i.e., in a locked cabinet within a locked office). Data stored on computers will be password protected and stored on a secure server behind each organization’s firewall. Each Research Team member has a unique network account and a secure password that complies with existing institutional policies and procedures. Only members of the team who are authorized by the site investigator leads will have access to secured files. Identities of participants will not be revealed in the publication or presentation of any results from this study.

Risks and Benefits to Participants

There is no known serious health or psychological risk of participating in this study. Some of the items in the self-report measures that ask respondents about their health, attitudes, and experiences could be considered sensitive. However, participants can refuse to answer questions at any time, which will be made clear during the consenting procedures and at the time of administration of all research measures and interviews. Minimal risks of study participation may still apply, such as participants feeling inconvenienced by the assessment requirements and/or uncomfortable or frustrated when responding to surveys or interviews. As with all research involving personal health information (PHI), there is also a potential risk of a breach of confidentiality for study participants. However, safeguards will be in place to decrease this risk to the fullest extent possible. Currently, there are no known risks associated with involvement in the study interventions, other than possible emotional discomfort associated with the discussion of issues related to complex health conditions. In instances where participants appear to be unduly distressed, they will be advised to speak directly with one of the study co-PIs.

All adverse events (e.g., mild distress following survey administration, breach of confidentiality) will be reported to the study co-PIs within 48 hours. The study team will ensure that each event is handled in the best interest of participants. If a serious adverse event (SAE) occurs, study team members will meet to discuss the event and its relevance to study participation. All SAEs will also be reviewed by the Data Safety and Monitoring Board (DSMB) as part of regularly scheduled meetings and procedures will be refined to prevent future events. Adverse events will be compiled and reported to the IRB as required.

There is a high likelihood that all study participants will benefit from the evidence-based components of care delivered through study interventions. Moreover, greater knowledge about the comparative effectiveness of the interventions and their impact on patient-centered outcomes will eventually benefit all patients hospitalized with sepsis, pneumonia or lower respiratory tract infection. For these reasons, we believe that the potential benefits of the knowledge to be gained from the proposed study outweigh the minimal risks posed to participants.

Compensation for Participation

Total possible compensation for the entire study: $65

- Time point 1: $20 for baseline self-report measures
- Time point 2: $20 for 3-month self-report measures
- Qualitative participant interview: $25

Study Oversight

Dr. Jatin Dave (Co-PI) and Dr. Sachin Yende (Co-PI) will be responsible for data and safety monitoring. Both will regularly meet with the entire study team to review all data protocols and policies, including informed consent and data confidentiality procedures. All key personnel will adhere to the National Institutes of Health (NIH) policy on education in the protection of human subject participants in the conduct of research. Additionally, we will convene biannual Data Safety and Monitoring Board (DSMB) meetings to ensure any issues related to participant or data safety are fully addressed. Interim data reports will be shared with the DSMB so they can provide feedback related to interim analyses, data quality and missingness. During these meetings, all unanticipated problems and adverse events will be discussed to obtain DSMB input.

The study protocol will be submitted to the University of Pittsburgh IRB. In addition, formal modifications will be submitted for any protocol changes to the University of Pittsburgh IRB for review and approval.

The Co-PIs and Stakeholder Co-I Dr. Rana Awdish will co-facilitate the stakeholder advisory board (SAB) meetings. The board is comprised of sepsis patients/caregivers, patient advocacy organizations, critical care providers, payers, and researchers/providers specializing critical care medicine. The board meets twice yearly to monitor study progress, provide feedback on study and intervention implementation and contributes to translation of study findings.

Conflict of Interest

The study investigators report having no conflicts of interest or financial interests related to the research conducted under this PCORI contract.

Dissemination

We will leverage the unique expertise of our Stakeholder Co-Investigator, SAB, and other partnering entities to support appropriate dissemination. Further, Erin Kelly, Senior Advisor, UPMC Health Plan, is supported by grant funds to produce relevant short-form content (e.g., blog posts, infographics, checklists, case studies) to share study results through appropriate audience-specific UPMC marketing channels. A comprehensive toolkit of strategies for optimal remote patient monitoring (RPM) and care team implementation will be developed to support dissemination. It will include lessons learned; implementation tools and resources; patient population-specific information; and strategies to

implement each intervention while considering variations such as delivery system/size, staffing requirements, payer support, and clinical workflows.

We will develop and maintain a plan that addresses data sharing of our research project's de-identified data with other researchers for future use in a manner that is appropriate for the nature of the research project data, and that is consistent with applicable privacy, confidentiality, and other legal requirements.

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