Statistical Analysis Plan for: Comparative Effectiveness of Readmission Reduction Interventions for Individuals With Sepsis or Pneumonia

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Summary

Study Population: Adults hospitalized for sepsis, lower respiratory tract or COVID-19 infection, age 21 and older with medium or 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 strategies (e.g., structured telephone support, low intensity remote patient monitoring (RPM) questions, high intensity RPM questions, standard call center response team, enhanced call center response team). 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: Anticipated enrollment: 1,668 individuals.

Interventions	• Structured Telephone Support • High Intensity Remote Patient Monitoring • Low Intensity Remote Patient Monitoring • Standard Team • Enhanced Team
Prognostic Strata	Analyses and response adaptive randomization are adjusted for prognostic stratification variables (illness severity and discharge to skilled nursing facility [1])
Predictive Strata	None
Evaluable Interactions	ACCOMPLISH is designed as a 2x2 factorial design testing 2 levels of RPM intensity crossed with 2 types of nurse response team.
Timing of Reveal	Randomization with delayed reveal of allocation
Domain-Specific Inclusions	Inclusion criteria include: • UPMC Health Plan member or patient with Medicare Fee-for-Service insurance • Treated at one of 18 prespecified hospitals for sepsis or lower respiratory tract infection, including COVID-19 • Age 21 or older • Medium or high-risk of readmission
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Admitted from setting other than home or independent living • Receiving hospice at time of admission • Being discharged on/to hospice or long-term acute care (LTAC) • Currently participating in UPMC Advanced Illness Care program • Unable to participate in RPM due to lack of technology/internet connection • Known pregnancy • Severe, persistent cognitive impairment • Patients with no documented PCP • Patients whose PCP disapproves of the patient potentially being enrolled in remote patient monitoring • Patients who are discharged from hospital to SNF and stay at the SNF for greater than 28 days
Intervention-Specific Exclusions	There are no intervention-specific exclusions.
Outcome measures	Primary endpoint: Post-Discharge Home Days at 90 days Secondary Domain-specific endpoints: • Functional status • Health-related quality of life • Transition to hospice • Emergent outpatient utilization • Readmissions • Mortality

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1. ABBREVIATIONS

ACCOMPLISH	Adaptive trial to test comparative effectiveness of readmission reduction approaches following infection and sepsis hospitalizations
ADI	Area Deprivation Index
AE	Adverse Event
CI	Confidence Interval
CER	Comparative Effectiveness Research
CRNP	Certified Registered Nurse Practitioner
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
ED	Emergency Department
HQL	Health-related Quality of Life
ICU	Intensive Care Unit
ITT	Intent-To-Treat
LRTI	Lower respiratory tract infection
MC FFS	Medicare Fee-for-Service
MCMC	Markov Chain Monte Carlo
OR	Odds Ratio
PCP	Primary care practitioner
PDHD	Post-Discharge Home Days
RPM	Remote Patient Monitoring
RAR	Response Adaptive Randomization
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
RPM	Remote Patient Monitoring
SAE	Serious Adverse Event
SNF	Skilled Nursing Facility
STS	Structured Telephone Support
UPMC	University of Pittsburgh Medical Center

2. DEFINITIONS

Care team: The individual or group of medical professionals whose role it is to screen RPM alerts and follow up with the patient, referring to the patient's PCP or other specialists if necessary.

Home: Level of residence or health care facility where the patient was residing prior to hospital admission.

Heterogeneity of Treatment Effects (HTE): The hypothetical scenario in which the effect of intervention on outcomes depends on baseline covariates.

Index Hospitalization: Hospitalization during which patient was enrolled in the clinical trial.

Intention To Treat (ITT): All eligible and consented patients who undergo randomization will be included in the ITT cohort for the purposes of analyzing the primary and secondary study outcomes.

Intervention arms: RPM-Low + Standard team, RPM-Low + Enhanced team, RPM-High + Standard team, RPM-High + Enhanced team.

Remote Patient Monitoring (RPM): An automatic electronic messaging system designed to push questions to patients at fixed intervals. Questions vary depending on the intensity of the RPM program (Low or High), but patient answers can trigger alerts and responses by members of the intervention care team.

Study day: The day of discharge to home is study day 0. The next calendar day is study day 1, etc.

Study hospital: Defined as the hospital where the patient was randomized and enrolled.

Study withdrawal: Defined as permanent withdrawal from study before completion of study activities. If a patient or surrogate requests withdrawal from the study, the clinician should seek explicit permission to continue data collection.

Prognostic strata: patient groups with different PDHD distributions.

Predictive strata: patient groups in which intervention effects are estimated individually.

3. BACKGROUND AND RATIONALE

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,[2] and older adults with multimorbidity are at higher risk.[3] Returning to the hospital after an index admission is shown to worsen patients' quality of life and increase their risk of healthcare-acquired infections,[4] despite the fact that many of these readmissions are avoidable.[5]

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.[6] Readmissions following sepsis and pneumonia are more common and associated with higher costs than readmissions due to heart failure, chronic obstructive pulmonary disease (COPD), or myocardial infarction.[2,6-10] Survivors of both conditions experience reduced quality of life, increased mortality and morbidity,[11-13] and cognitive impairment and functional limitations.[14-16] 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.[7-9,11,17] 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 half of readmissions after sepsis can be attributed to preventable causes[18] 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.[19] Most patients hospitalized with sepsis or pneumonia are >65 years of age and have multimorbidity.[20,21] Two-thirds of readmissions following sepsis or pneumonia were due to infection (~40%) and cardiovascular (15%) and respiratory disease (10%).[22] 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.[23,24]

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.[25] Among these, more complex interventions that leverage multiple components and multiple care providers have greater effect on maintaining patients at home longer after discharge.[25] Specific successful model components include care coordination/care management activities and patient self-management education.[26,27]

A key priority for the health care system is understanding how to effectively deploy the post-acute workforce in the community.[28,29] 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 and 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.[30] 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.[31] Provider monitoring of symptom exacerbation is important because patients alone are unreliable in reporting worsening symptoms.[26,32] RPM platforms have received FDA approval, reduced readmissions in multiple observational and randomized controlled studies, and are routinely used in clinical care.[26,33] 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,[34-36] the reason for which may be that studies often fail to define specific intervention components.[37] 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.[38,39] However, this approach is resource intense and may be difficult to scale across large geographic areas.[40] 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.[41] 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.[42]

4. ENROLLMENT CRITERIA

4.1. *Population*

This domain enrolls adults hospitalized for sepsis or lower respiratory tract infection, including COVID-19, age 21 and older, medium or high-risk of readmission, and whose primary outpatient physician is willing to participate in RPM.

4.2. *Eligibility criteria*

Patients are eligible for this domain if they meet all of the REMAP-level inclusion and none of the REMAP-level exclusion criteria (see Core Protocol Section 6.4). Patients who may be eligible for the REMAP may have conditions that may exclude them from the ACCOMPLISH Domain.

4.2.1. Inclusion criteria for this domain

Patients will be included in this domain if they meet the following criteria:

- UPMC Health Plan member or patient with Medicare Fee-for-Service insurance
- Treated at one of 19 prespecified hospitals for sepsis or lower respiratory tract infection
- Age 21 or older
- Medium or high-risk of readmission

4.2.2. Exclusion criteria from this domain

Patients will be excluded from this domain if they have any of the following:

- Admitted from setting other than home or independent living
- Receiving hospice at the time of admission
- Being discharged on/to hospice or LTAC
- Currently participating in UPMC Advanced Illness Care Program
- Unable to participate in RPM due to lack of technology/internet connection
- Known pregnancy
- Severe, persistent cognitive impairment
- No documented primary care physician (PCP)
- PCP disapproves of the patient potentially being enrolled in remote patient monitoring

5. INTERVENTIONS

ACCOMPLISH tests the impact of a set of active arms compared with standardized telephone support (STS):

- Structured **Telephone Support (STS):**[30] Structured telephone support (STS) consists of post-discharge assessment, education, and medication reconciliation delivered telephonically by a case manager, home care as needed, and follow-up appointment with the primary care within seven days post-discharge.

The following types of interventions are used across the active arms:

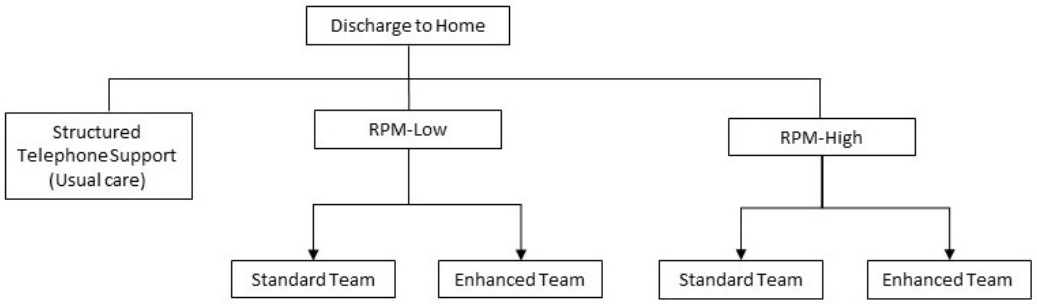
- **Low-intensity Remote Patient Monitoring (RPM-Low):**[43] Questions are pushed to members three times per week for up to 90-days post-discharge. Questions are limited to those checking vital signs that indicate worsening of infection. Patient answers RPM questions, which trigger high or medium alerts and a response by members of the intervention care team (see below).
- **High-intensity** Remote **Patient Monitoring (RPM-High):**[23] Questions are pushed to members three 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, which trigger high or medium alerts and a response by members of the intervention care team (see below).
- **Standard Team**: [41,44] RPM alerts are screened by a nurse-staffed call center. Nurses determine whether immediate outreach to the member is warranted and facilitate connection to the appropriate care (such as referring the member to their PCP, specialist, or instructing the patient to go the emergency department).
- **Enhanced Team**: [27,38,45] RPM alerts are screened by a nurse-staffed call center and alert a certified registered nurse practitioner (CRNP) to modify care plans. CRNPs, who operate in a palliative care role, have prescribing authority and will also facilitate connection to the appropriate care. In addition to reacting to RPM triggers, CRNPs and other members of an interdisciplinary palliative care team (e.g., social workers, nurses) meet with the patient in-person or virtually at least three times in 90 days, conduct assessments, develop care plans, and complete a physician order for life-sustaining treatment.

Patients are randomized to either STS, or active arm; if randomized to active arm, they are assigned to 1 level of RPM (RPM-Low or RPM-High) and 1 type of care team (standard or enhanced care team), leading to 4 active intervention arms:

- RPM-Low + Standard Team
- RPM-Low + Enhanced Team
- RPM-High + Standard Team
- RPM-High + Enhanced Team.

A graphical representation of the interventions is shown in Figure 1.

Figure 1: Study Design



5.1. *Timing of initiation of interventions*

Participants will be enrolled in the appropriate intervention (as randomized) by their first full week day home from the hospital or skilled nursing facility (SNF). Participants enrolled in a RPM arm will be contacted by a research coordinator by telephone and encouraged to download the RPM application and initiate the program. If enrolled in structured telephone support, they will receive a post-discharge phone call per usual care timing.

5.2. *Duration of remote interventions*

The duration of standard telephone support will align with usual care, but is expected to be limited to one brief telephone conversation, in most cases. The duration of remote patient monitoring interventions is 90 days.

5.3. *Concomitant care*

The intent of this trial is to observe participants as they participate in real-world post-discharge health care. Therefore, there are very few concomitant care restrictions. Remote patient monitoring pathways will be paused during hospital readmissions and/or admissions to other inpatient care settings. The RPM program will be stopped if the study team learns that a patient entered hospice or expired. Most of other health care utilization will be observed and analyzed during analysis.

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. Participants who are known to be currently participating in the Advanced Illness Care program will be excluded from study recruitment. 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 during the three month study intervention period. 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.

6. ENDPOINTS

6.1. *Primary endpoint*

The primary efficacy endpoint will be post-discharge home-days (PDHD) recorded over the first 90 days after discharge to the patient's home. Patients will be assigned -1 days if they die before day 90 post-discharge home. Among patients who survive 90 days or more, PDHD is recorded as the total number of days alive and out of acute care hospitals or post-acute care facilities (e.g., inpatient rehabilitation, skilled nursing facilities, long-term care facility). If a patient is readmitted to one of these facilities during the 90 days after returning home, then those days not at home will be subtracted from their PDHD. The following rules will be used to calculate PDHD.

- Home is defined as any location that does not involve insurance claims charged to UPMC Health Plan. This can include the patient's own residence, someone else's residence (family or friend), independent living facility or personal care home. It is not restricted to being the same location at which the patient resided pre-admission, so long as it does not involve UPMC Health Plan claims.
- The index hospitalization and post-acute health care facilities (e.g., long-term acute care facility, ventilator-rehabilitation unit, rehabilitation facility, transitional care units, skilled nursing care, nursing homes) visited following discharge are counted as "hospitals" until the patient is discharged home.
- PDHD can take on integer values from -1 to 90. Any calendar day partially spent in acute care hospitals or post-acute care facilities is counted as a full day for the purposes of calculating PDHD, regardless of whether it was part of the initial admission or any readmission.

6.2. *Secondary endpoints*

The domain-specific secondary outcome measures are:

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.[46] 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.[47]

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.[48]

Transition to Hospice: will be assessed via claims data at 90 days to see if members 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.

7. TRIAL CONDUCT

7.1. *Data collection*

Quantitative data will be collected from several sources. Self-report assessments will be gathered at baseline and 90 days post discharge using REDCap Cloud, a secure data collection platform. Clinical data, additional patient demographic/descriptive information, and health care utilization data will be extracted from electronic health records and payer claims at baseline and 90-days. These data collection procedures have been used previously by our site teams (e.g., successfully retaining over 80% of participants in other large-scale studies). For individuals who withdraw from the study, data will be retained up to the point of study withdrawal.

Qualitative telephone interviews will be conducted to understand patient or caregiver intervention-related experiences. We will conduct the interviews as soon as possible following the 90-day follow-up to maximize participants recall related to involvement in the study. We will conduct interviews with 120 patients (30 patients from each of the 4 intervention arms). If a patient is unable to participate in an interview due to medical complexity, we will attempt to interview his/her primary caregiver. All audio recordings of interviews will be transcribed by experienced qualitative researchers and de-identified. We will 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 will 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 will be iterative and will take place over the course of the qualitative data collection period. For example, we will review transcripts from the first few patient interviews to begin developing a codebook and to make needed modifications to our interview guide for subsequent interviews. A separate codebook will 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 will assess inter-rater reliability using percent agreement and kappa scores. Upon acceptable interrater reliability, the qualitative research team will thematically code all qualitative documents.

7.2. *Blinding*

All study staff will be blinded to the adaptive intervention arm randomization probabilities. Study Co-Principal Investigators, Co-Investigators, and employed (non-consultant) statisticians will be blinded to the participant enrollment totals per named intervention arm. Teams caring for the patients (e.g., primary care physicians) will be unblinded to the interventions. All study staff will be completely unblinded after data collection is complete.

8. STATISTICAL ANALYSIS PLAN

8.1. *Statistical Objectives*

The following objectives and endpoints are relevant to the final statistical analysis of the ACCOMPLISH trial.

Primary analyses

- For Aim #1, the primary analyses will be to compare PDHD between the 5 study arms (STS and the 4 experimental intervention arms):
    - **Aim 1a**: Efficacy will be evaluated by comparing PDHD between the STS arm and each of the 4 experimental arms, adjusting for illness severity (mechanical ventilation + vasopressors) and discharge location (whether patient went to SNF prior to home) and accounting for multiple comparisons
    - **Aim 1b**: Superiority of each experimental arm over the others will be evaluated by calculating the posterior probability that PDHD for each arm is greater than the others, adjusting for illness severity

(mechanical ventilation + vasopressors) and discharge location (whether patient went to SNF prior to home).

Secondary analyses

- To compare each intervention arm to STS, and to each other, with respect to mortality and PDHD among survivors.
- To determine the effects of each intervention arm and STS on secondary endpoints:
    - Functional status as measured by the PROMIS Physical Function—for Mobility Aid Users[46]
    - Health-related Quality of Life (HQL) as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire-SF (QLESQ-SF) [48]
    - Transition to Hospice. Defined as whether the patient transitioned to hospice care.
    - Emergent outpatient care utilization. Defined as the count of urgent outpatient visits (ED visits and urgent visits).
    - Readmission. Defined as subsequent admission after index admission.
    - Mortality. Whether a patient dies during the first 90 days post discharge to home
- To explore potential heterogeneity of treatment effect

8.2. *Intervention delivery*

8.2.1. Intervention data

Data relating to the completion of intervention components will be summarized for each intervention arm separately. Intervention completion requires the cooperation of up to 3 components: automatic (computer generated) notifications, follow-up by the remote monitoring team (possibly in response to the automatic notification), and patient completion of follow-ups initiated automatically or by the response team.

The following RPM data will be collected:

- Number of RPM questionnaires sent to patients
- Number of RPM questionnaires completed by patients
- Number of yellow and red alerts sent to the monitoring team
- Number of yellow and red alerts addressed by the monitoring team within the appropriate time period
- Number of attempted in-person or virtual visits by the CRNP to the patient (enhanced team arms only)
- Number of medication reviews (enhanced team arms only)
- Number of documented advance directive/POLST discussions conducted (enhanced team arms only)

8.2.2. Intervention fidelity

Patients completing a minimum of intervention components (as outlined in section 8.2.1 above) will be considered as having followed the protocol for their intervention arm.

8.3. *Bayesian adaptive design elements*

8.3.1. Statistical modeling

The primary analysis is a Bayesian ordinal logistic regression model that accounts for differences in the 90-day PDHD depending on two patient strata that were significantly associated with outcomes in this population in a retrospective analysis of UPMC data (see Appendix): 1) illness severity (defined as patient needing ventilation or vasopressors), and 2) whether the patient was discharged to a SNF after they leave the hospital and prior to their discharge home. Treatment effects are modeled as a factorial where independent variables for RPM level (low or high) and type of team (standard or enhanced) are modeled with an interaction. The model assumes proportional treatment effects across the levels of the ordinal home days endpoint.

8.3.2. Bayesian ordinal logistic regression

The primary analysis employs a Bayesian cumulative logistic regression assuming proportional odds effects. Let $Y_i \in \{-1, 0, 1, \dots, 89, 90\}$ be the primary ordinal 90-day home days endpoint for patient i. Let γ_{ij} denote the probability of patient *i* observing a home days endpoint of j or lower. For $j = -1, \dots, 89$, the primary analysis model is formulated as:

$$\begin{aligned}\text{logit}(\gamma_{i,j}) = \alpha_j - (X_{i1}(\theta_1 + \theta_2 X_{i2} + \theta_3 X_{i3} + \delta X_{i2} X_{i3}) \\ + \beta_1 Z_{i1} + \beta_2 Z_{i2} + W_{i,COV}\,\boldsymbol{\kappa})\end{aligned} \quad (1)$$

where $\text{logit}(\gamma_{ij}) = \log\left(\frac{\gamma_{ij}}{1-\gamma_{ij}}\right)$ are the log odds of the probability that Y_i is less than j. The variables, X_{i1}, X_{i2}, X_{i3}, are indicators for treatment assignment, where $X_{i1} = 1$ when randomized to one of the 4 care model interventions (interventions 2-5 above) and 0 when randomized to the STS arm, X_{i2} = 1 when randomized to an intervention with RPM high and $X_{i2} = 0$ for RPM low, X_{i3} =1 when randomized to an intervention with enhanced team and $X_{i3} = 0$ for standard team. The model is formulated such that STS is considered the referent treatment and all parameters learned in the model are in relation to STS. The four care models are modeled as a factorial comprised of the level of RPM and type of team deployed.

The parameters $\theta_1, \theta_2, \theta_3$ are log odds ratios for active interventions and the parameter, δ, is an interaction effect between RPM high and enhanced team. We assume that the effects of each intervention are constant across strata and can be explained by a proportional log-odds ratio shift in the home days distribution. Each intervention's treatment effect is made up of components of the parameters, such that the treatment effect for RPM low/standard is equal to θ_1,

the effect for RPM high/standard is equal to $\theta_1 + \theta_2$, the effect for RPM low/enhanced is equal to $\theta_1 + \theta_3$, and the effect for RPM high/enhanced is equal to $\theta_1 + \theta_2 + \theta_3 + \delta$. We report these treatment effects as odds ratios, where $OR_1 = \exp(\theta_1)$ is the odds ratio for RPM low/standard, $OR_2 = \exp(\theta_1 + \theta_2)$ is the odds ratio for RPM high/standard, $OR_3 = \exp(\theta_1 + \theta_3)$ is the odds ratio for RPM low/enhanced, and $OR_4 = \exp(\theta_1 + \theta_2 + \theta_3 + \delta)$ is the odds ratio for RPM high/enhanced. The model is parameterized such that an odds ratio greater than 1 indicates that the care model is beneficial compared to STS.

The variables, Z_{i1} and Z_{i2}, are indicators of disease strata for patient i, where $Z_{i1} = 1$ when a patient has severe illness (spent time on mechanical ventilation or vasopressors while hospitalized) and $Z_{i1} = 0$ otherwise, and $Z_{i2} = 1$ if patient i has been discharged to a SNF and $Z_{i2} = 0$ if the patients is discharged immediately to home. With the above model, we assume that the underlying distribution of home days is different within each stratum, and that those differences can be explained by a proportional log-odds ratio shift in the home days distribution through the parameters, β_1 and β_2.

Finally, p additional covariates, $W_{i,COV}$, are included in the model with parameters, $\boldsymbol{\kappa}$. W_{COV} contain indicator variables for time at randomization, measured in buckets of 3-month intervals. The first time bucket (furthest in past) will be used as the referent in the model.

8.3.3. Model priors

The prior distribution of α_j is specified on the probability scale:

$$\alpha_j = \text{logit}\left(\sum_{k=-1}^{j} \pi_k\right), j = -1, \ldots, 89$$

where

$$\pi_{-1}, \ldots, \pi_{90} \sim \text{Dirichlet}(\phi_{-1}, \ldots, \phi_{90});$$

with hyperparameters, ϕ_j, specified based on the observed rates of home days across all states in pre-trial data (see Appendix) and providing 1 patient's worth of information so that $\sum_{h=-1}^{90} \phi_h = 1$. The vector $\boldsymbol{\phi}$ consists of concentration parameters with a weight of 0.133 on -1 (death), 0.005 on 0-19 (split evenly), 0.017 on 20-39 (split evenly), 0.017 on 40-49 (split evenly), 0.026 on 50-59 (split evenly), 0.042 on 60-69 (split evenly), 0.077 on 70-79 (split evenly), 0.228 on 80-89 (split evenly), and 0.454 on 90.

Because of the large ordinal scale, it is likely that some levels of the ordinal endpoint will be quite sparse. By using a prior centered on UPMC patient data, we help to guard against model instability issues on levels without observations early in the trial when fewer patients have been enrolled. The prior is parameterized to be weakly informative, such that as more patients are enrolled, the patient data quickly overwhelms the prior in the posterior estimation.

For each stratum-specific log odds ratio, we place a normal prior distribution with mean 0 and standard deviation of 1:

$$\beta_l \sim N(0,1), l = 1,2.$$

Additionally, for the covariates' log odds ratios, $\boldsymbol{\kappa}$, we specify the same normal distributed prior with mean 0 and standard deviation 1:

$$\kappa_k \sim N(0,1), k = 1,2,\ldots,p-1.$$

This standard normal prior on the log odds ratio induces a relatively non-informative prior on the odds ratio that is lognormally distributed with a prior median of 1 (no effect). The prior assumes there is a 95% probability that the odds ratio effect is between 0.14 and 7.10.

We specify independent, normally distributed priors on the log-odds treatment effects:

$$\theta_t \sim N(0,1), t = 1,2,3.$$

This prior on the log odds ratio induces a relatively non-informative prior on the odds ratio that is lognormally distributed with a prior median of 1 (no effect). The prior assumes there is a 95% probability that the odds ratio effect is between 0.14 and 7.10.

For the interaction term, δ, we use the following prior:

$$\delta \sim N(0,\tau^2),$$

with the following prior on the variance term of the interaction:

$$\tau^2 \sim IG(0.8, 0.0525).$$

This inverse-gamma prior for τ^2 was chosen to encourage dynamic borrowing when learning the interaction term, δ. This prior allows the data to determine the amount of information that is borrowed from the two individual interventions (RPM High and Enhanced team). If τ^2 is close to zero, then there is an additive effect for the combination arm with RPM high and Enhanced team; if τ^2 is positive, then we assume a synergistic effect between RPM high and the Enhanced team (effect of the combination is greater than the sum of the two interventions); if τ^2 is negative, this assumes an antagonistic interaction (effect of the combination is less than the sum of the two interventions). The prior shape 0.8 and prior scale 0.0525 were chosen such that the prior for τ^2 has a median of 0.1 with 90% probability of being less than 1.

8.3.4. Model Stability

To assure model stability in the primary analysis model, the following modeling conventions may be taken at the statistical analysis committee's discretion.

- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the outcome 11 never occurred, then a combined outcome of 10 & 11 will be modeled for the analysis.
- If a time bucket category has fewer than 5 patients observed in the category, it will be combined with the adjacent bucket (more recent bucket).

8.4. *Posterior summaries*

The following statistical quantities are used in the design of the trial. The posterior distribution of all model parameters is calculated using MCMC. The algorithm allows the generation of M (ex. 100,000) draws from the joint posterior distribution for all model parameters.

8.4.1. Evaluation of posterior estimates

The Bayesian model of the primary endpoint described above is fitted to the data at each interim analysis. The posterior is calculated as:

$$p(\varphi|Y) \propto \prod_{i=1}^{n} p\,(Y_i|\varphi)p(\varphi),$$

where φ is the set of parameters for the primary endpoint model, $p(\varphi)$ is the prior for those parameters, Y_i is the primary endpoint value for each patient, and n is the number of patients. The posterior is evaluated using MCMC using statistical software Stan.

8.4.2. Probability of arm superiority over other intervention arms

For each of the four care model arms, we calculate the probability an arm is superior to other active arms using the posterior probability that each arm is optimal. This quantity is calculated from the M samples of the posterior distribution of the effect of each arm by reporting the proportion of posterior samples in which the odds ratio for arm *t* is the maximum observed effect across all non-STS treatment arms, t=1,…,4:

$$O(t) = \frac{1}{M}\sum_{m=1}^{M} I\left[OR_t < OR_j, \quad for\ all\ j \neq t\right], \quad t = 1, \ldots, 4.$$

8.4.3. Probability of arm superiority over STS

To determine if the trial is successful at the final analysis, we summarize the posterior probability that each care model arm is superior to STS. The probability of superiority is calculated as the proportion of the M samples of an intervention's OR treatment effect that are greater than 1:

$$O(t) = \frac{1}{M}\sum_{m=1}^{M} I[OR_t > 1], \qquad t = 1 \ldots,4.$$

8.4.4. Probability of harm

To determine if an arm is futile at an interim analysis, we summarize the posterior probability that each care model arm is harmful compared to STS. The probability of harm is calculated as the proportion of the M samples of an intervention's OR treatment effect that are less than 1:

$$O(t) = \frac{1}{M}\sum_{m=1}^{M} I[OR_t < 1\}, \qquad t = 1 \ldots,4.$$

8.5. *Proportional odds assumption*

The ordinal logistic regression model assumes that the effect of a treatment on the odds of higher PDHD is the same for all levels of the outcome. For example, this assumption entails that the effect of an intervention on the odds of surviving through the 90-day post discharge period increases by an amount proportional to the odds of having greater than 80 PDHD. In the event that the interventions have no effect on survival, but a beneficial effect on PDHD among survivors, the proportionality assumption will be violated.

8.5.1. Assessing the proportional odds assumption

Assessment of the proportional odds assumption will occur once all patients are enrolled, or the study is ended for futility of one or more active arms over STS. We will dichotomize the endpoint at each level of the PDHD outcome, summarizing the odds ratio for each dichotomization and plotting for visual inspection of equality. Meaningful shifts in odds ratios across the ordinal scale will be interpreted as evidence of non-proportionality.

8.5.2. Extending the proportional odds model

To assess the proportional odds assumption around the lower end of the distribution, we propose the following non-proportional model in Equation (2):

$$\text{logit}(\gamma_{i,j}) = \alpha_j - \left(X_{i1}(\theta_{1,k} + \theta_{2,k}X_{i2} + \theta_{3,k}X_{i3} + \delta_k X_{i2}X_{i3}) + \beta_1 Z_{i1} + \beta_2 Z_{i2} + W_{i,COV}\,\boldsymbol{\kappa}\right), \qquad k = -1, \geq 0. \qquad (2)$$

where we allow the treatment effect to vary for death ($k = -1$) and stay constant across the home-days distribution (0-90). The effects for strata are constant across the full scale, -1:90.

This proposed model results in the probability of death for patients on STS equal to:

$$\Pr(Y_i = -1) = logit^{-1}(\alpha_{-1} - (\beta_1 Z_{i1} + \beta_2 Z_{i2} + W_{i,COV}\,\boldsymbol{\kappa}))$$

And the probability of death for patients on a treated arm:

$$\Pr(Y_i = -1) = logit^{-1}\Big(\alpha_{-1} - \big(X_{i1}(\theta_{1,-1} + \theta_{2,-1}X_{i2} + \theta_{3,-1}X_{i3} + \delta_{-1}X_{i2}X_{i3}) + \beta_1 Z_{i1} + \beta_2 Z_{i2} + W_{i,COV}\,\boldsymbol{\kappa}\big)\Big).$$

Then the remainder of the 90-day home days scale can be described using the usual proportional odds shift, for $j = 1, \ldots, 89$:

$$\Pr(Y_i \le j) = logit^{-1}\Big(\alpha_j - \big(X_{i1}(\theta_{1,\geq 0} + \theta_{2,\geq 0}X_{i2} + \theta_{3,\geq 0}X_{i3} + \delta_{\geq 0}X_{i2}X_{i3}) + \beta_1 Z_{i1} + \beta_2 Z_{i2} + W_{i,COV}\,\boldsymbol{\kappa}\big)\Big).$$

The priors will be the same as specified in Section 8.3.3 for each level of the log-odds treatment effects, θ_k.

The qualitative interpretation of this model will be similar to the primary analysis model above; however, this formulation will allow us to assess how these interventions impact mortality versus the time at home.

Analyses of mortality and PDHD among survivors from the model in equation (2) will be considered separate secondary analyses. See Section 8.9.3 below.

8.6. *Timing of interim analyses*

The first interim analysis will occur when 250 patients have been followed for 90 days and have observed their 90-day PDHD. Subsequent interims will occur every 3 months until the total sample size has been enrolled, using data collected from all patients for whom days from randomization has elapsed and their 90-day PDHD has been recorded.

At each interim, response adaptative randomization (RAR) allocation probabilities will be updated according to the details described in Section 8.7

8.7. *Randomization*

Initial randomization is set so that 30% of patients are randomized to STS and 70% of patients are randomized equally to the remaining 4 arms. After a burn-in of 250 patients, RAR will begin. The allocation to STS will be maintained at 30% throughout the course of the trial. The remaining 70% of patients will be allocated to the 4 active arms preferentially based on the probability that the intervention is superior to the other active arms as defined in Section 8.4.2.

8.8. *Futility stopping*

The interventions selected for this proposal have been used in clinical care for other conditions (e.g., heart failure) and not shown to harm patients. Furthermore, RAR ensures that a higher proportion of patients randomized to one of the four intervention arms are randomized to the better-performing arms based on the results of the interim analyses. Thus, the likelihood of harm in our trial is low.

We considered the rare scenario that an arm performs worse than usual care, for which RAR will not change the allocation ratios. We therefore included a rule where an arm would be discontinued if the posterior probability of harm (odds ratio for home days <1) is >90%:

$$\text{Futility rule: } \Pr(OR < 1) > 0.9.$$

Based on preliminary simulations, we expect enrolling ~1200 patients before harm in this scenario is detected. Our simulations also ensured that our rule would prevent an arm to be dropped prematurely and likely to show benefit at the end of the trial.

Futility checking will occur at all interim analyses except the first to allow sufficient patient accrual into each treatment arm, preventing some probability of false declaration of futility. Futility is assessed separately for each individual care model arm. Declaration of futility for a particular arm during an interim analysis will trigger an early stopping of randomization to that arm, pending review by the DSMB. If all active arms are dropped for futility, then the entire trial would conclude early. The trial would conclude at the interim at which the final active arm was dropped. Our futility rule was selected by evaluating the operating characteristics of several rules via simulation (See Appendix, Section 12.5).

8.9. *Analytic approach*

Analyses described in this section pertain to the statistical analysis conducted at the conclusion of the ACCOMPLISH trial, after all data have been collected.

8.9.1. Final analysis of primary endpoint

The primary analysis of PDHD will consist of the posterior probability of superiority of each active arm over STS following posterior calculation from the model in Section 8.9.1. Success will be declared at the final analysis when all patients have observed their primary endpoint if the posterior probability of any care model relative to STS is greater than 0.991. This threshold was determined through simulation to assure the type I error is controlled at a 2.5% level. Specifically, we simulated 10,000 trials under the null scenario and find the threshold that controls overall 2.5% type I error (probability of declaring success under the null) across the simulated trial scenarios (Appendix Table 4).

We will also calculate the posterior probability that each active arm is superior to the other active arms (Section 8.4.2).

8.9.2. Additional analysis of primary endpoint

We will also estimate the marginalized effects of RPM low and RPM high compared to STS, and alternatively Standard team and Enhanced team compared to STS. These effects will be estimated in models blinded to one or the other intervention modality. For instance, to estimate the effects of RPM low and RPM high compared to STS, we will use the following modification of model (1):

$$\text{logit}(\gamma_{i,j}) = \alpha_j - (X_{i1}(\theta_1 + \theta_2 X_{i2}) + \beta_1 Z_{i1} + \beta_2 Z_{i2} + W_{i,COV}\,\boldsymbol{\kappa}) \quad (3)$$

The variables, X_{i1}, X_{i2} are indicators for treatment assignment, where $X_{i1} = 1$ when randomized to one of the 4 care model interventions and 0 when randomized to the STS arm, X_{i2} = 1 when randomized to an intervention with RPM high and $X_{i2} = 0$ for RPM low. The parameters θ_1, θ_2 are log odds ratios for active interventions; the treatment effect for RPM low/standard is equal to θ_1, the effect for RPM high/standard is equal to $\theta_1 + \theta_2$. An equivalent model will be used to estimate the effects of Standard team and Enhanced team type compared to STS.

From these models, we will estimate the prosterior probability that the intervention odds ratio is greater than one, and the appropriate posterior probability of superiority comparing interventions in the same model.

8.9.3. Final analysis of mortality and PDHD among survivors

Analysis of mortality and PDHD among survivors will be conducted jointly via the model in Section 8.5.2. This model relaxes the proportional odds assumption, allowing for the effect of interventions on mortality to be independent of the effect on PDHD among survivors. From this model, we will estimate the following posterior probabilities:

- Posterior probability of superiority of each active arm over STS with respect to probability of survival to 90 days
- Posterior probability that each active arm is superior to the other active arms with respect to probability of survival to 90 days
- Posterior probability of superiority of each active arm over STS with respect to PDHD among survivors
- Posterior probability that each active arm is superior to the other active arms with respect to PDHD among survivors

8.9.4. Final analysis of inpatient hospital readmissions

Analyses of inpatient hospital readmission will be performed using a Bayesian proportional odds model similar to the one used in section 8.3.3, but with ordinal outcome taking values of -1 for non-survivors to 90 days, 0 for survivors who were readmitted within 90 days, and 2 for survivors who were not readmitted within 90 days. We will first assume that the odds ratios of interventions are proportional across all levels of this outcome. Due to the similarity between readmission and PDHD outcomes, we will use all model priors from the model in 8.3.3 in the analysis of readmissions. From this model, we will estimate the following posterior probabilities:

- Posterior probability of superiority of each active arm over STS with respect to probability of readmission or death to 90 days
- Posterior probability that each active arm is superior to the other active arms with respect to probability of readmission or death to 90 days

When mortality rates are low, the treatment effects estimated above will approximately equal to the effect on readmission prior to death. However, when mortality rates are high this may not be true[49]. We will therefore also estimate the effect of readmission prior to death on survival to 90 days directly using the (frequentist) Fine and Gray subdistribution hazard model. Coefficients in the linear predictor of this model will mimic the form of the linear predictor in the model of 8.3.3 (minus the intercept terms), including terms for each intervention, the interaction, calendar time if necessary, and relevant risk predictors. From this model, we will estimate the following quantities:

- Difference in cumulative incidence functions for readmission at 90 days and their 95% confidence intervals, for each intervention compared to STS
- Difference in cumulative incidence functions for readmission at 90 days and their 95% confidence intervals, for each intervention compared to other active intervention arms.

8.9.5. Final analysis of ordinal outcomes truncated by death

PROMIS and HRQoL are continuous outcomes collected around day 90 after discharge conditional on survival. Similarly, number of emergency visits by day 90 depends on having 90 days of follow up to be comparable between different treatment arms. Thus, to avoid selection bias we will analyze of these 3 outcomes using a similar composite outcome approach used for the primary outcome, wherein death before day 90 will be treated as the worst outcome on an ordinal scale otherwise consisting of the natural values taken by these variables. For PROMIS and HRQoL, which take positive values, deaths will be assigned a value of -1. For number of emergency visits by day 90, which also takes positive values up to the largest number of visits observed in the sample (K visits), deaths will be assigned a value of K+1. We will use a Bayesian proportional odds model to analyze these outcomes, similar to the approach of the primary analysis in 8.3.3. In our models, each unique value taken by these outcomes will receive its own intercept, a way of modeling continuous outcomes that is competitive with linear regression[50] but which allows us to account for death. The linear predictor of our model will otherwise mimic that of the primary analysis in 8.3.3. From these models, we will estimate the following quantities:

- Posterior probability of superiority of each active arm over STS in terms of surviving with better functional outcomes (PROMIS and HRQoL), or fewer emergency visits within 90 days.
- Posterior probability of superiority of each active arm over all other active arms in terms of surviving with better functional outcomes (PROMIS or HRQoL), or fewer emergency visits within 90 days.

In the event that mortality rates are very small, or that the effect of interventions on mortality rates are very small, we will perform a survivors-only analysis of these endpoints, which is likely to be minimally biased under these conditions[49]. In these cases, we will analyze these endpoints among survivors to 90 days post-discharge. When modeling these endpoints, we will use Bayesian linear (for PROMIS and HRQoL) or generalized linear (number of emergency visits by 90

days) regression with uninformative priors. The linear predictors of these models will mimic that of the primary analysis in 8.3.3. From these models, we will estimate the following quantities:

- Posterior probability of superiority of each active arm over STS in terms better functional outcomes (PROMIS and HRQoL), or fewer emergency visits within 90 days, among survivors.
- Posterior probability of superiority of each active arm over all other active arms in terms of better functional outcomes (PROMIS or HRQoL), or fewer emergency visits within 90 days, among survivors.

8.9.6. Final analysis of hospice care

Analysis of admission to hospice care will be performed using Bayesian Logistic regression with uninformative priors. The endpoint will be defined as any admission to hospice by day 90 post-discharge; any hospice care will be considered a successful outcome, while death within 90 days or survival without hospice care will be considered as non-successful outcome. The linear predictors the model will mimic that of the primary analysis in 8.3.3. From this model, we will estimate the following quantities:

- Posterior probability of superiority of each active arm over STS in terms larger odds of admission to hospice within 90 days.
- Posterior probability of superiority of each active arm over all other active arms in terms larger odds of admission to hospice within 90 days.

8.9.7. Sensitivity analyses exploring the potential impact of payer type

On August 10, 2022 the trial expanded its inclusion criteria to include Medicare Fee-For-Service (MC FFS) patients. We will conduct two types of sensitivity analyses to detect any differences in PDHD distribution between UPMC Health Plan and MC FFS patients:

- We will fit two additional proportional logit models accounting for payer type:
    - One logit model including a term for payer which will capture proportional shifts in home days across payer groups; and
    - 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.
- 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. We will also explore limiting these analyses to data collected after August 10, 2022 when MC FFS patients were eligible.

8.9.8. Sensitivity analysis limited to UPMC Health Plan members with coverage for the duration of follow up

We will conduct an analysis limited to patients with UPMC Health Plan coverage throughout the duration of the 90-day follow up period. FFS patients, as well as UPMC Health Plan members who lose or drop their coverage under the Plan before the end of the 90-day follow up period, will be excluded from this analysis. Outcomes ascertainment could be more accurate among patients included in this analysis. This analysis will be conducted using the model in 8.3.3.

8.10. *Analyses of heterogeneity of treatment effect*

8.10.1. Comparison group determination for heterogeneity of effect analysis

Because it is possible for our RAR design to reduce enrollment to under-performing arms, we may be at a power disadvantage for identifying heterogeneity of treatment effect (HTE) of each active intervention compared with STS as a function of baseline covariates: age, sex, race, chronic comorbidity index, comfort with technology, health literacy level, Area Deprivation Index, discharge location, illness severity and admitting diagnosis. Therefore, we may pool arms prior to HTE analysis based on arms' average effects. For instance, if both RPM-Low and RPM-High are on average effective, we will pool these patients. However, we may choose not to pool patients by care team component (Standard Team or Enhanced Team) since resource utilization for these components is different and stakeholders have expressed a strong interest in identifying subgroups that benefit, especially among those who receive the Enhanced Team component. Thus, all analyses described below will be repeated for comparisons between each active (and potentially pooled) intervention and STS arms.

8.10.2. Analysis of effect heterogeneity across pre-determined subgroups

We will conduct differential treatment effects analyses, comparing differences between RPM groups and STS across pre-specified subgroups of patient-level clinical, social, and environemntal factors that could be potentially used to tailor service delivery. All analyses will be performed using a cumulative logit model for the primary PDHD outcome, including terms for treatment arm, subgroup, treamtent by subgroup interactions, stratification variables, and calendar time of randomization. Subgroup variables and definitions were determined as plausibly related to treatment effect heterogeneity. Each subgroup variable will be analyzed in two ways: 1) four RPM arms kept separate; and 2) comparing standard team and enhanced team arms. Analyses will not be adjusted for multiple comparisons. Evidence of differential treatment effects across subgroup levels will be summarized using the posterior probability that interaction terms are greater than 0. In addition, treatment effects by subgroup level will be summarized using the posterior median cumulative odds ratios from each model, and corresponding 95% credible intervals.

Subgroup definitions are as follows:

- Patient Age
    - <65 vs age >=65

- Sex
    - Female vs male
- Race
    - White patients vs Black patients
- Chronic Condition index
    - CCI<5 vs CCI>=5
- Level of comfort with technology
    - Comfortable vs uncomfortable vs missing
- Health literacy level
    - Limited vs marginal vs adequate vs missing
- State-ranked Area Deprivation Index
    - Quartile 1 vs quartile 2 vs quartile 3 vs quartile 4 vs missing
- Location after discharge
    - Skilled Nursing Facility vs home
- Severity of illness
    - Severe (mechanical ventilation or vasopressor use during index hospitalization) vs not severe
- Discharge diagnosis
    - COVID vs Non-COVID Sepsis vs Other lower respiratory tract infection

8.10.3. Analysis of effect heterogeneity on dichotomized outcomes

We will explore potential heterogeneity of the effects of active arms compared to control groups after dichotomizing the PDHD outcome, collapsing all values of PDHD less than 90 into a single category. This will facilitate the estimation of conditional average treatment effects on the risk difference scale [52].

For our first set of analyses, we will dichotomize continuous or ordinal covariates, and analyze the conditional absolute risk differences (cARD) between the levels of the dichotomized covariates. For each covariate, we will test the null hypothesis that there is no difference in the cARDs using the Q test [53]. We will also calculate 95% CI for the cARDs and their differences.

For our second set of analyses, we will use an "effect-based" approach to estimate ARDs conditional on multiple covariates simultaneously[54]. In this approach, we will divide the data into two halves in approximately equal proportion. The first half will be used for cARD model derivation, as well as any missing data imputation models. We will compare the performance of several competing cARD models with different advantages and disadvantages, including causal forest, local linear random forest R-learners, and regularized logistic regression[55-57]. We will compare these models in the derivation set using the following cross-validated performance metrics: area under the target operating characteristic

curve (AUTOC) and R-loss[58]. The model with the best performance will be validated in the patients that were not used for model derivation. Model validation will be performed by examining the calibration of the model, including the estimation of calibration intercept, slope, and their 95% Cis[59]. The presence of HTE identified by the model will be determined if the calibration slope p-value is <0.05. In addition, we will estimate ARDs and 95% CIs within quantiles of predicted cARDs generated from the derived model for each patient in the validation set. We will test the null hypothesis that the quantile ARDs are not monotonically increasing across the quantiles[59]. Finally, to examine whether the results are dependent on the particular random derivation/validation split that was used, we will repeat the analyses across many different random splits and aggregate the results, including inferences, with the result from the original random split[59]. If we are able to identify HTE using our selected best-performing cARD prediction model, we will determine the value of the predicted cARD that serves as the best classification rule for identifying the subgroup that benefits from each candidate intervention.[60] Finally, we will explore which baseline characteristics predict treatment effectiveness by plotting the associations between baseline characteristics against cARD predictions, and a fit-the-fit approach using binary decision trees where the predicted cARD is treated as the outcome variable.[61]

8.11. *Handling of missing data*

8.11.1. Missing PDHD data

The primary endpoint is ascertained using claims data for the majority of patients, and medical records review for the small subset of patients that either drop UPMC Health Plan coverage during the course of follow up, or are covered by the Medicare Fee-for-Service program. We will assume that no record of death or readmissions counted against the primary endpoint correctly correspond to the absence of these events for the patient, and therefore the primary outcome will be completely observed for all patinets.

8.11.2. Missing data for secondary endpoints and baseline covariates

For binary and normally-distributed secondary endpoints as well as baseline covariates with missing data, we will generate 10 completed datasets via a Multiple Imputation with Chained Equations (MICE) algorithm for the secondary and sensitivity analyses specified.[62] MICE draws missing data values from a sequence of fully-specified regression models. We will use logistic regression models for modeling missing binary data, and normal linear regression otherwise. The linear predictor for each regression model will include linear terms for the primary outcome (PDHD), all secondary outcomes, and all baseline covariates, in addition to first-order interactions with each intervention arm.

Once generated, we will use the 10 completed datasets to fit the appropriate analysis models, performing final aggregated estimation and inference using Rubin's rules.[62]

For the primary analysis, we will impute any missing baseline covariates based on the following logic:

- If the patient is missing a value for the severe illness indicator, we will impute the value to 0 (not severe).
- If the patient is missing a value for discharge location, we will impute the value to 0 (home).

We expect minimal missing baseline covariates (<1%) so are choosing imputation rules that are designed around the most likely categories given a value is missing.

8.12. *Type 1 error rate*

Success is declared at the final analysis when all patients have observed their primary endpoint if the posterior probability of any care model relative to STS is greater than 0.991. This threshold was determined through simulation to assure the type I error is controlled at a 2.5% level (see Appendix). Specifically, we simulate 10,000 trials under the null scenario and find the threshold that controls overall 2.5% type I error (probability of declaring success under the null) across the simulated trials.

9. ETHICAL CONSIDERATIONS

9.1. *Data Safety and Monitoring Board*

The DSMB will provide oversight for the trial.

9.2. *Potential domain-specific adverse events*

This study is expected to pose minimal risk. The STS intervention is used for patients recovering from sepsis, LRTI, and other diseases. RPM interventions used in this domain are commonly used as routine care for other diseases. As a result, anticipated adverse events (AE) will be uncommon and include mild distress following survey administration and breach of confidentiality. Other AEs will be reported only where, in the opinion of the co-Principal Investigators, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 12). Additionally, it is expected that a high proportion of critically ill patients who will be enrolled in this trial will experience mortality, substantial morbidity and readmissions. These endpoints are included in the primary and secondary endpoints. Stopping rules in the rare scenario that an intervention worsens these endpoints are included in the Statistical Appendix and data regarding the primary endpoint stratified by intervention and select secondary endpoints will be provided to the DSMB.

9.3. *Domain-specific consent issues*

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 comprehension and cognitive screener. If the subject 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 screeners) 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 subject consenting to participation. Consent for the qualitative interviews will also be obtained during this process.

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.

10. FUNDING

10.1. *Funding of domain*

The ACCOMPLISH domain is funded by the Patient Centered Outcomes Research Institute, contract #IHS-2019C1-16055.

10.2. *Funding of domain interventions*

The STS and RPM interventions in the ACCOMPLISH domain are funded by UPMC.

10.3. *Domain-specific declarations of interest*

All investigators involved in REMAP Post-Acute Care ACCOMPLISH domain maintain a declaration of conflicting interests with the Patient-Centered Outcomes Research Institute.

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12. Appendix

12.1. *Sepsis data for simulations*

To create realistic clinical trial simulations, we obtained pre-trial member-level data from UPMC for patients that were hospitalized from either sepsis, pneumonia, and/or a lower respiratory infection. Patients in this sample were at least 21 years old and deemed low risk for readmission (based on an internal UPMC risk score). We received 4718 records from members that received their insurance through Medicare or commercial plans. This data included the following covariates: age group, CCI, sepsis status, pneumonia status, LRTI status, whether a patient had mechanical ventilation, vasopressors, or was in the ICU. In addition, we have whether a patient was discharged to a SNF or to home, as well as their home days endpoint score. We additionally received 2737 records from members whose insurance is through Medicaid or SNP (special needs population). This data only contained the home days endpoint with no additional covariate information.

Using the totality of this data, we summarize the home days distribution by finding the proportion in each level of the outcome, as shown in the "Overall" column in Figure 2.

In addition, we summarize the two strata variables using the partial data with covariate information. We define the severe strata as patients who were on mechanical ventilation or vasopressors during their hospital stay. In this data, 11% of the population meets this definition. We define the SNF population as patients whose discharge status was "Discharge to SNF", where 37% of the population meet this definition. Using these covariates, we estimate the relationship between the home days endpoint and the covariates, illness severity and discharge to SNF, using a frequentist ordinal regression. We estimate an odds ratio for severe illness compared to non-severe of 0.75 and an odds ratio for patients discharged to SNF compared to those discharged home to be 0.35. Under these estimated odds ratios, we transform the home days distribution (using the full data) for the severe strata and the discharged to SNF strata. The resulting distributions are presented in Figure 2. Patients who are not categorized as severe or were discharged straight to home are assumed to have the baseline home days distribution shown in the overall column.

Strata variables were chosen empirically by evaluating the covariates that best explained patient heterogeneity in the data. These two variables were identified as major risk factors for this patient population using the provided data, therefore, were critical to control baseline characteristics.

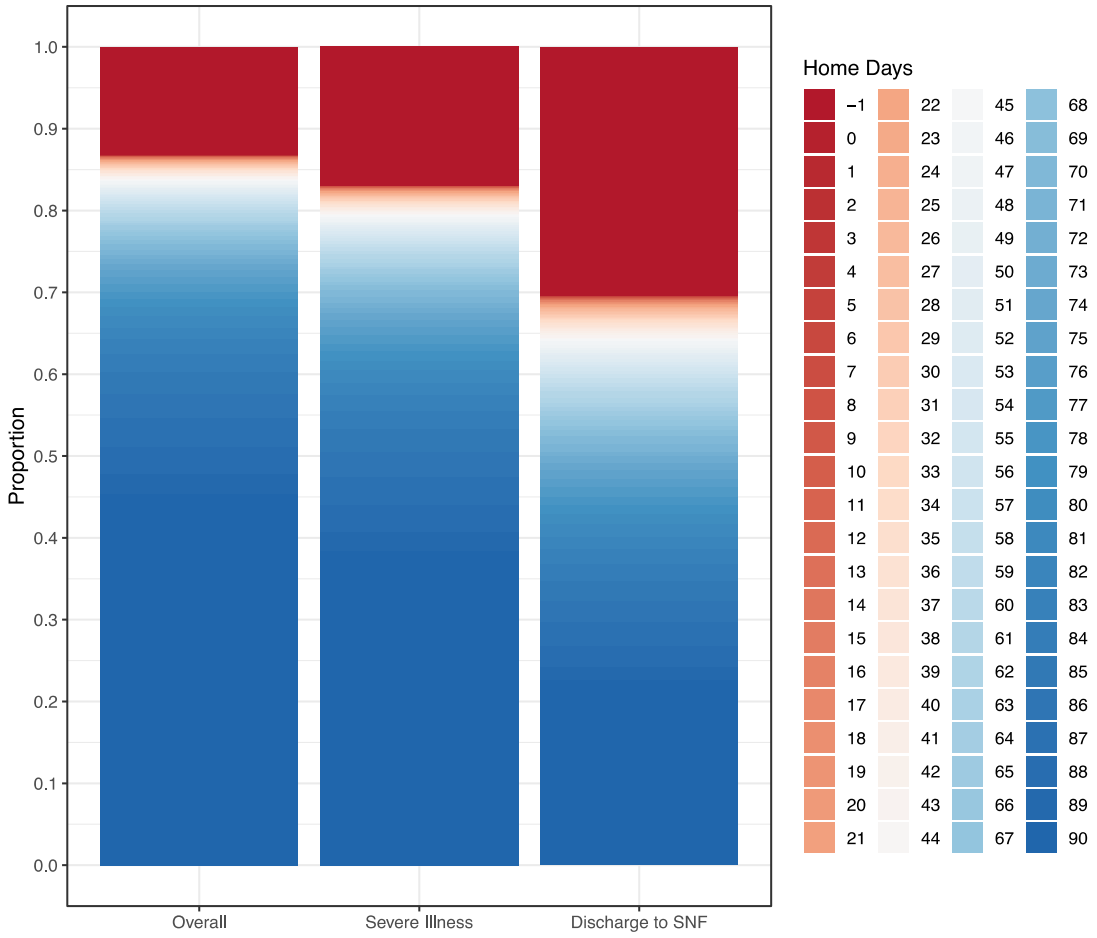


Figure 2: Distribution of home days endpoint using UPMC member level data.

12.2. *Virtual patient simulation*

In these simulations, we simulate a maximum total sample size of 1500 patients assuming no patient dropout. For each simulation, we assume the ACCOMPLISH trial will enroll 11% of patients that are in the severe strata and 37% of patients that are discharged to SNF (using proportions from the observed data). We simulate the strata by drawing from two independent Bernoulli variables with probability 11% for the severe strata variable and 37% for the SNF variable. These strata are not mutually exclusive such that a patient may be both severe and discharged to SNF. Based on a patient's strata assignment, we shift the overall home days distribution using the odds ratios of 0.75 and 0.35 for severe and discharged to SNF strata, respectively. If a patient is both severe and discharged to SNF, their home days distribution is shifted with an odds ratio of 0.26 ($\exp(\log(0.75) + \log(0.35))$). We do not incorporate the additional covariates (age categories) into the simulations since we do not expect age to influence the treatment effect and therefore the operating characteristics of the trial.

To simplify the simulations, we assume a collapsed distribution of home days. Table 2 shows the collapsed distribution for the baseline population.

Table 2. Collapsed home days distribution for the baseline population

Death	0-19	20-39	40-49	50-59	60-69	70-79	80-89	90
0.133	0.005	0.017	0.017	0.026	0.042	0.077	0.228	0.454

For patients in strata, this distribution is then shifted based on the ORs described above.

12.3. *Simulated treatment effect scenarios*

We assume proportional odds treatment effects for each care model under different patterns of efficacy. Table 3 presents the scenarios in terms of the OR on each of the 4 care models. Table 4 summarizes the endpoint for each stratum under each of these assumed OR treatment effects.

Table 3. Treatment effect scenarios

		RPM low + Standard	RPM high + Standard	RPM low + Enhanced	RPM high + Enhanced
1	Null	1.0	1.0	1.0	1.0
2	One Weak	1.0	1.0	1.0	1.25
3	One Expected	1.0	1.0	1.0	1.5
4	One Strong	1.0	1.0	1.0	1.75
5	Two Weak	1.0	1.25	1.0	1.25
6	Two Expected	1.0	1.5	1.0	1.5
7	Two Strong	1.0	1.75	1.0	1.75
8	All Weak	1.25	1.25	1.25	1.25
9	All Expected	1.5	1.5	1.5	1.5
10	All Strong	1.75	1.75	1.75	1.75
11	All Weak, Combo Additive	1.25	1.25	1.25	1.56
12	All Expected, Combo Additive	1.5	1.5	1.5	2.25
13	All Strong, Combo Additive	1.75	1.75	1.75	3.06

Table 4. Summary of PDHD distribution under different treatment effect scenarios*.

	Median PDHD	Probability of Mortality	Probability of 90 PDHDs
OR = 1.00			
Baseline	90 (82, 90)	0.13	0.45
Severe	88 (79, 90)	0.17	0.38
Discharged to SNF	84 (70, 90)	0.31	0.23
OR = 1.25			
Baseline	90 (84, 90)	0.11	0.51
Severe	90 (81, 90)	0.14	0.44
Discharged to SNF	86 (72, 90)	0.26	0.27
OR = 1.50			
Baseline	90 (85, 90)	0.09	0.55
Severe	90 (83, 90)	0.12	0.48
Discharged to SNF	97 (75, 90)	0.23	0.30
OR = 1.75			
Baseline	90 (86, 90)	0.08	0.59
Severe	90 (84, 90)	0.11	0.52
Discharged to SNF	87 (77, 90)	0.20	0.34

**For a clinical perspective, assume a length of stay of readmission is 5 days. To achieve an OR of 1.5 in the baseline group (nonsevere illness, discharged home), at least 25% of these patients must experience an increase in PDHD from 82 to 84, corresponding to ~0.5 fewer readmissions.*

12.4. *Accrual*

We simulate patient accrual from a Poisson process assuming an average accrual rate of 70 patients per month until the maximum sample size of 1500 with complete 90-day follow-up is achieved.

12.5. *Operating characteristics when assumptions are met*

For each of the scenarios described in Table 3, we simulate 1000 trials with and without the futility rule and characterize the behavior across trials. The null scenarios are summarized with 10,000 simulated trials.

Under each treatment effect scenario, we report the following operating characteristics in Table 5.1 for results without the futility rule and Table 5.2 for results with the futility rule:

- Probability of success overall and per arm (e.g., power or type I error)
- Probability of futility overall and per arm
- Mean number of subjects enrolled per arm and in total

- Probability each arm is selected as best
- Average bias for each arm (calculated as estimated OR (using posterior median) – true OR for each arm)

Tables 5.1 and 5.2 abbreviate the names of the interventions to 1-4, where 1 = RPM low/Standard, 2 = RPM high/Standard, 3 = RPM low/Enhanced, 4 = RPM high/Enhanced.

Under the null scenario (with and without futility), the overall simulated type I error (defined as any active arm declaring success in the null scenario) is about 2.3%. The average number of patients enrolled on each care model is between 249-268 patients and all arms have about an equal (~25%) probability of being declared the best care model. The average bias for each arm is -0.03 (similar regardless of futility).

The following discussion focuses on the results including the futility rule. Table 5.1 is there for reference, though notably we see essentially no power loss when the futility rule is used compared to no futility. Under the presented scenarios, trials rarely stop prior to the maximum sample size. The column summarizing the average total sample size of the trial is provided to understand the impact of the futility rule. Under the null scenario, the average total sample size is 1482 when the futility rule is used, with a 4.7% probability that the trial stops early for futility. Each arm has about a 25% chance of being stopped for futility at one of the interim analyses.

Rows 2-4 show scenarios where only intervention 4 (RPM enhanced/standard) is effective. In these scenarios, arm 4 enrolls on average 457, 607, and 695 patients under the three assumed treatment effect strengths. Arms 1, 2 and 3 enroll around 200 patients under the weak treatment effect, around 150 for the moderate treatment effect, and around 120 for the strong treatment effect. When there is a single effective intervention, the design appropriately enrolls more patients onto the stronger arm and reduces allocation to the weaker arms. This is also seen in the summary of the probability of selecting arm 4 as the best arm, which is around 99% when the treatment effect is expected or strong. The power for the effective arm (4) is 29.9% under a weak effect, 85.1% under the expected effect, and 98.6% under the strong effect. The type I error rate on the non-effective interventions (1, 3, 4) is less than 0.025. The overall power for these scenarios is 30.8%, 85.1%, and 98.7% under the weak, expected, and strong treatment effect, respectively. The average bias is minimal for these scenarios with all arms observing bias less than 0.10 in both directions for all treatment effect strengths.

In scenarios 5-7 when interventions 2 and 4 are effective, the overall power increases to 41.7%, 91.8%, and 99.5% under the weak, expected, and strong treatment effect, respectively. The per arm power is 24.9% for arm 2 and 27.3% for arm 4 under a weak treatment effect, 71.2% for arm 2 and 72.5% for arm 4 under the expected treatment effect, and 90.4% and 92.2% for arm 2 and 4 under the strong treatment effect. The ineffective arms (1 and 3) have type I errors that are less than 2.5%. The average bias is minimal for all arms under all treatment effects.

In scenarios 8-10 when the treatment effects are the same across all arms, allocation is consistent across the care models, with around 250-270 patients per arm. The probability of being selected as the best arm is also approximately 25% for each of the four care models. Power per arm under the expected treatment effect is about 60%, and the overall probability of finding a successful arm (overall power) is 95%. Power per arm under the strong treatment effect is about 80%, and the overall probability of finding a successful arm (overall power) is 99.9%.

In the final scenario, when all arms are effective, but intervention 4 has an additive benefit, power for arm 4 is 81% under the weak treatment effect and greater than 99% for the expected and strong treatment effect. The probability of being superior to STS (power) for Arm 2 and 3 are about 20% for the weak effect, 50% for the expected effect and about 76% for the strong effect. Arm 1 has about 20-30% lower power in this scenario compared to arms 2 and 3 despite the arms all being simulated with the same treatment effect. The model underestimates the effect of arm 1, with an average bias between -0.07 in weak scenario to -0.16 in the strong scenario. Overall power for these scenarios is 86.5% under the weak treatment effect and 100% for both the expected and strong treatment effect. The design appropriately finds the best arm 85% of the time under the weak effect and about 99% of the time under the expected and strong treatment effect.

Table 5.1 Operating characteristics per intervention without futility

Scenario		Mean N						Success					Prob Selected Best				Bias			
		STS	1	2	3	4	Total	1	2	3	4	Overall	1	2	3	4	1	2	3	4
1	Null	450	253	262	266	266	1500	0.005	0.006	0.007	0.007	0.023	0.247	0.244	0.258	0.251	-0.03	-0.03	-0.02	-0.03
2	One Weak	450	178	206	208	458	1500	0.006	0.009	0.011	0.299	0.308	0.038	0.056	0.052	0.854	-0.04	0.01	0.01	-0.01
3	One Expected	450	130	156	158	607	1500	0.001	0.014	0.006	0.847	0.847	0.006	0.002	0.001	0.991	-0.06	0.03	0.04	-0.01
4	One Strong	450	104	128	124	694	1500	0.004	0.009	0.013	0.987	0.988	0.001	0	0	0.999	0.06	-0.02	-0.07	0.05
5	Two Weak	450	157	358	160	375	1500	0.009	0.252	0.007	0.269	0.416	0.014	0.472	0.012	0.502	-0.01	-0.02	-0.01	-0.02
6	Two Expected	450	109	410	111	420	1500	0.004	0.713	0.003	0.726	0.919	0.002	0.473	0	0.525	0.00	-0.02	-0.01	-0.02
7	Two Strong	450	91	427	92	440	1500	0.002	0.903	0.004	0.923	0.996	0	0.485	0	0.515	0.00	-0.02	-0.02	-0.02
8	All Weak	450	253	258	266	273	1500	0.189	0.188	0.213	0.213	0.498	0.244	0.246	0.268	0.242	-0.03	-0.03	-0.02	-0.02
9	All Expected	450	245	267	266	272	1500	0.562	0.595	0.601	0.603	0.952	0.217	0.274	0.257	0.252	-0.05	-0.04	-0.03	-0.04
10	All Strong	450	243	262	272	272	1500	0.823	0.817	0.852	0.843	0.999	0.231	0.236	0.274	0.259	-0.04	-0.04	-0.02	-0.03
11	All Weak, Combo Additive	450	175	206	210	458	1500	0.113	0.206	0.215	0.808	0.864	0.053	0.052	0.047	0.848	-0.07	0.01	0.01	-0.03
12	All Expected, Combo Additive	450	125	163	162	599	1500	0.301	0.554	0.551	0.997	1.000	0.004	0.004	0.006	0.986	-0.12	0.04	0.04	-0.02
13	All Strong, Combo Additive	450	106	132	134	678	1500	0.500	0.778	0.801	1.000	1.000	0.000	0.000	0.000	1.000	-0.16	0.09	0.11	-0.02

Table 5.2 Operating characteristics per intervention with futility

Scenario		Mean N						Success/Futility					Prob Selected Best				Bias			
		STS	1	2	3	4	Total	1	2	3	4	Overall	1	2	3	4	1	2	3	4
1	Null	451	249	257	262	263	1482	0.006/ 0.252	0.006/0.257	0.006/0.249	0.006/ 0.267	0.023/ 0.047	0.247	0.24	0.261	0.252	-0.03	-0.03	-0.03	-0.03
2	One Weak	450	176	204	205	457	1492	0.006/ 0.270	0.009/0.186	0.011/0.175	0.299/ 0.055	0.308/ 0.018	0.042	0.053	0.057	0.848	-0.05	0.01	0.01	-0.02
3	One Expected	450	128	156	157	607	1498	0.001/ 0.279	0.014/0.144	0.006/0.131	0.851/ 0.011	0.851/ 0.006	0.007	0.003	0.001	0.989	-0.06	0.03	0.04	-0.01
4	One Strong	450	104	128	124	695	1500	0.004/ 0.321	0.009/0.120	0.013/0.135	0.986/0 .006	0.987/ 0.004	0.001	0	0	0.999	-0.08	0.06	0.05	-0.01
5	Two Weak	451	156	357	158	375	1496	0.009/ 0.202	0.249/0.047	0.007/0.197	0.273/ 0.043	0.417/ 0.010	0.019	0.468	0.01	0.503	-0.01	-0.02	-0.01	-0.01
6	Two Expected	450	109	410	111	420	1500	0.004/ 0.180	0.712/0.004	0.003/0.192	0.725/ 0.003	0.918/ 0.002	0.002	0.476	0	0.522	0	-0.02	-0.01	-0.02
7	Two Strong	450	91	427	92	440	1500	0.002/ 0.180	0.904/0.004	0.004/0.193	0.922/ 0.003	0.995/ 0.002	0	0.486	0	0.514	0	-0.02	-0.01	-0.02
8	All Weak	450	253	258	266	272	1499	0.190/ 0.034	0.190/0.041	0.213/0.039	0.213/ 0.050	0.500/ 0.004	0.243	0.248	0.267	0.242	-0.03	-0.03	-0.02	-0.02
9	All Expected	450	245	267	266	272	1500	0.562/ 0.016	0.595/0.006	0.601/0.020	0.603/ 0.009	0.952/ 0.001	0.217	0.274	0.257	0.252	-0.05	-0.04	-0.04	-0.04
10	All Strong	450	243	262	272	272	1500	0.823/ 0.003	0.817/0.004	0.852/0.002	0.843/ 0.002	0.999/ 0.000	0.231	0.236	0.274	0.259	-0.04	-0.04	-0.02	-0.03
11	All Weak, Combo Additive	450	175	206	210	458	1500	0.113/ 0.051	0.205/0.037	0.216/0.036	0.808/ 0.013	0.865/ 0.001	0.052	0.052	0.048	0.848	-0.07	0.01	0.01	-0.03
12	All Expected, Combo Additive	450	125	163	162	599	1500	0.301/ 0.017	0.554/0.008	0.551/0.011	0.997/ 0.002	1.000/ 0.001	0.004	0.004	0.006	0.986	-0.12	0.04	0.04	-0.02
13	All Strong, Combo Additive	450	106	132	134	678	1500	0.500/ 0.007	0.778/0.004	0.801/0.002	1.000/ 0.000	1.000/ 0.000	0	0	0	1	-0.16	0.09	0.11	-0.02

Power Calculations 11/24/2023

There is a possibility that full enrollment will not be feasible. In this section we illustrate the power that may be obtained in each of the scenarios above at sample sizes of 1200 to 1500 complete, with 1500 complete replicating the results shown above in the “with futility” tables. For the N=1500 column, taken from the table above, the results were computed via trial simulation. For the remaining columns, approximations were employed reflecting the information

fractions available at 1200 to 1450 complete patients. We expect these approximations to be close, but they are likely to be slightly aggressive, meaning that if they are off they are likely to overestimate power. We do not expect needed sample sizes to be off by more than ~25 patients.

Note that similar to the above tables, the table below shows sample sizes of complete patients. At present, the trial is observing 2.5% of patients lost to followup, significantly fewer than originally estimated. Nevertheless, to obtain a given number of complete patients, we must enroll a larger number. For example, to obtain 1350 complete patients with 2.5% loss to followup, we need to enroll 1350/(1-0.025) = 1385 patients total.

Scenario	N=1200	N=1250	N=1300	N=1350	N=1400	N=1450	N=1500	N Needed for 80% power (if feasible)
1, Null	~0.025	~0.025	~0.025	~0.025	~0.025	~0.025	0.023	NA
2, One Weak	0.256	0.265	0.274	0.282	0.291	0.299	0.308	NA
3, One Expected	0.765	0.782	0.798	0.812	0.826	0.839	0.851	1308
4, One Strong	0.963	0.969	0.974	0.978	0.981	0.984	0.987	<1000
5, Two Weak	0.347	0.359	0.371	0.382	0.394	0.406	0.417	NA
6, Two Expected	0.850	0.864	0.877	0.889	0.899	0.909	0.918	1049
7, Two Strong	0.982	0.985	0.988	0.990	0.992	0.994	0.995	<1000

8, All weak	0.418	0.432	0.446	0.460	0.474	0.487	0.500	NA
9, All Expected	0.900	0.911	0.921	0.930	0.938	0.946	0.952	<1000
10, All Strong	0.994	0.996	0.997	0.998	0.998	0.999	0.999	<1000
11, All weak combo additive	0.782	0.798	0.814	0.828	0.841	0.854	0.865	1255
12, All expected combo additive	>0.997	>0.998	>0.998	>0.999	>0.999	>0.999	1.000	<1000
13, All strong, combo additive	>0.997	>0.998	>0.998	>0.999	>0.999	>0.999	1.000	<1000

12.6 Operating characteristics when assumptions are violated

As noted in Section 8.5, it is possible that the interventions have differential effects on patients who would have died within 90 days had they been assigned to SRS compared to those who would have survived. This type of differential effect of treatment for different types of patients violates the proportional odds assumption from the ordinal logistic regression model. Therefore, we provide operating characteristics for simulations in which patient data are generated under non-proportional assumptions. In these scenarios, we leave the probability of death unchanged regardless of the treatment effect and shift the remaining portion of the home-days endpoint (0-90) by the scenario specific OR. See Figure 2 for a visual representation of the treatment effect on the baseline probability distribution under these non-proportional assumptions.

Table 6 shows the population characteristics under a range of odds ratios for these two scenarios, for each of the 3 population subsets. Odds ratios in Table t reflect the effect of interventions on home days among survivors only.

Table 6. Summary of PDHD distribution under different treatment effect scenarios*, when proportionality of effect of intervention is violated

	Median PDHD Among Survivors (IQR)	Probability of Mortality	Probability of 90 PDHDs
OR=1.00			
Baseline	90 (82, 90)	0.13	0.45
Severe	88 (79, 90)	0.17	0.38
Discharged to SNF	84 (70,90)	0.30	0.23
OR=1.25			
Baseline	90 (84, 90)	0.13	0.50
Severe	90 (82, 90)	0.17	0.43
Discharged to SNF	86 (74, 90)	0.30	0.26
OR=1.50			
Baseline	90 (85, 90)	0.13	0.54
Severe	90 (84, 90)	0.17	0.47
Discharged to SNF	87 (76, 90)	0.30	0.29
OR=1.75			
Baseline	90 (86, 90)	0.13	0.57

Severe	90 (85, 90)	0.17	0.50
Discharged to SNF	88 (79, 90)	0.30	0.32

**For a clinical perspective, assume a length of stay of readmission is 5 days. To achieve an OR of 1.5 in the baseline group (non-severe illness, discharged home), at least 25% of these patients must experience an increase in PDHD from 82 to 84, corresponding to ~0.5 fewer readmissions.*

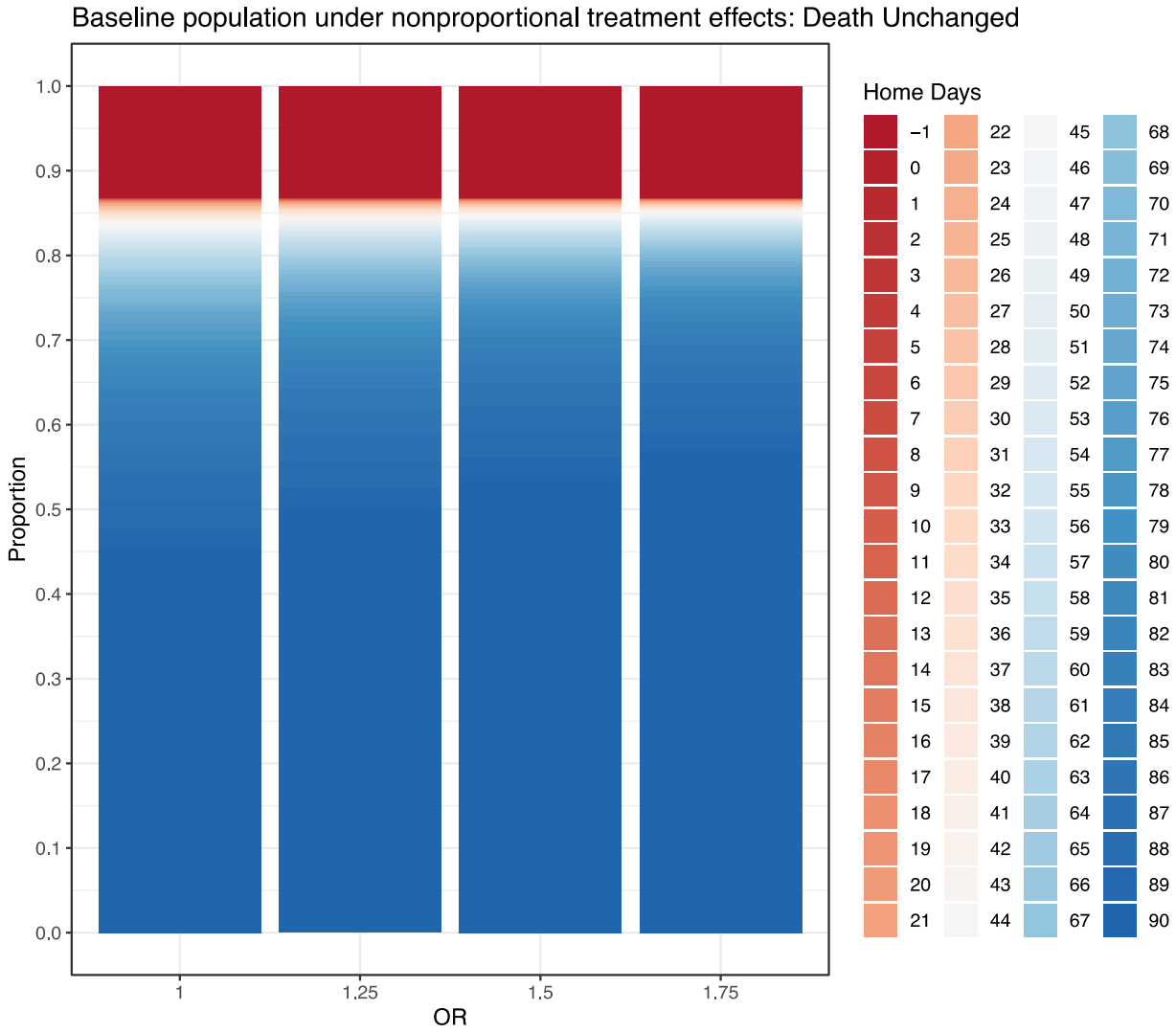


Figure 3: Distribution of home days endpoint using UPMC member level data showing non-proportional shifts where the probability of death is unchanged and the effect of the OR is applied only to 0-90 values on the scale.

For all scenarios outlined in Table 5, we repeat the simulations under these non-proportional assumptions. The simulations are summarized in the same manner as above in Tables 7.1 and 7.2, displaying results without futility and with futility, respectively.

Table 7.1 Operating characteristics per intervention without futility under non-proportional assumptions																				
Scenario		**Mean N**						**Success**					**Prob Selected Best**				**Bias**			
		STS	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Overall**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1	Null	450	253	262	266	266	1500	0.005	0.006	0.007	0.007	0.023	0.247	0.244	0.258	0.251	-0.03	-0.03	-0.02	-0.03
2	One Weak	450	206	233	236	376	1500	0.002	0.006	0.01	0.085	0.095	0.107	0.124	0.11	0.659	-0.04	-0.01	0	-0.13
3	One Expected	450	174	201	202	472	1500	0.005	0.012	0.003	0.338	0.341	0.05	0.052	0.041	0.857	-0.05	0	0	-0.25
4	One Strong	450	143	178	173	556	1500	0.001	0.013	0.01	0.615	0.617	0.006	0.014	0.015	0.965	-0.06	0.02	0.02	-0.38
5	Two Weak	450	190	331	196	333	1500	0.005	0.078	0.005	0.083	0.146	0.061	0.429	0.054	0.456	-0.02	-0.13	-0.02	-0.12
6	Two Expected	450	149	374	152	376	1500	0.004	0.287	0.003	0.287	0.473	0.019	0.501	0.008	0.472	-0.01	-0.25	-0.02	-0.26
7	Two Strong	451	121	396	125	408	1500	0.004	0.543	0.003	0.555	0.774	0	0.476	0.001	0.523	-0.01	-0.38	-0.01	-0.37
8	All Weak	449	256	262	267	266	1500	0.07	0.060	0.060	0.076	0.208	0.255	0.244	0.252	0.249	-0.13	-0.14	-0.13	-0.13
9	All Expected	450	257	261	265	267	1500	0.221	0.231	0.238	0.232	0.581	0.258	0.243	0.263	0.236	-0.26	-0.26	-0.25	-0.26
10	All Strong	450	253	258	270	268	1500	0.404	0.410	0.421	0.423	0.838	0.241	0.236	0.266	0.257	-0.4	-0.4	-0.39	-0.4
11	All Weak, Combo Additive	450	209	233	236	373	1500	0.07	0.071	0.073	0.341	0.423	0.135	0.117	0.127	0.621	-0.15	-0.12	-0.11	-0.29
12	All Expected, Combo Additive	451	174	205	211	458	1500	0.141	0.21	0.222	0.838	0.903	0.046	0.043	0.059	0.852	-0.31	-0.24	-0.23	-0.69
13	All Strong, Combo Additive	450	153	183	195	518	1500	0.197	0.374	0.398	0.954	0.989	0.024	0.024	0.031	0.921	-0.47	-0.36	-0.35	-1.23

	Table 7.2 Operating characteristics per intervention with futility under non-proportional assumptions																			
Scenario		**Mean N**						**Success/Futility**					**Prob Selected Best**				**Bias**			
		STS	**1**	**2**	**3**	**4**	**Total**	**1**	**2**	**3**	**4**	**Overall**	**1**		**2**	**3**	**4**	**1**	**2**	**3**	**4**
1	Null	451	249	257	262	263	1482	0.006/ 0.252	0.006/ 0.257	0.006/ 0.249	0.006/ 0.267	0.023/ 0.047	0.247	0.24	0.261	0.252		-0.03	-0.03	-0.03	-0.03
2	One Weak	450	201	229	233	375	1487	0.002/ 0.281	0.006/ 0.211	0.01/ 0.186	0.087/ 0.109	0.097/ 0.034	0.114	0.122	0.119	0.645		-0.04	-0.01	0	-0.13
3	One Expected	451	173	200	200	473	1497	0.005/ 0.253	0.012/ 0.164	0.003/ 0.163	0.342/ 0.051	0.345/ 0.011	0.052	0.052	0.039	0.857		-0.05	0	0	-0.26
4	One Strong	452	141	177	172	556	1498	0.001/ 0.295	0.013/ 0.156	0.01/ 0.166	0.622/ 0.022	0.624/ 0.008	0.007	0.015	0.016	0.962		-0.07	0.02	0.02	-0.38
5	Two Weak	452	188	330	194	332	1497	0.005/ 0.233	0.077/ 0.090	0.005/ 0.234	0.083/ 0.101	0.145/ 0.015	0.059	0.433	0.059	0.449		-0.02	-0.13	-0.02	-0.13
6	Two Expected	450	149	374	151	377	1500	0.004/ 0.192	0.287/ 0.030	0.003/ 0.211	0.290/ 0.032	0.475/ 0.003	0.02	0.499	0.008	0.473		-0.01	-0.25	-0.02	-0.26
7	Two Strong	450	120	396	124	407	1498	0.004/ 0.171	0.544/ 0.016	0.003/ 0.193	0.554/ 0.020	0.775/ 0.003	0	0.479	0.001	0.52		-0.01	-0.38	-0.01	-0.37
8	All Weak	450	255	261	265	265	1496	0.069/ 0.084	0.06/ 0.087	0.060/ 0.079	0.075/ 0.090	0.206/ 0.008	0.251	0.249	0.252	0.248		-0.13	-0.14	-0.13	-0.13
9	All Expected	450	257	261	265	267	1500	0.220/ 0.037	0.231/ 0.028	0.237/ 0.027	0.232/ 0.040	0.579/ 0.001	0.256	0.244	0.264	0.236		-0.26	-0.26	-0.25	-0.26

10	All Strong	450	252	258	270	268	1499	0.403/ 0.030	0.41/ 0.029	0.422/ 0.028	0.423/ 0.028	0.837/ 0.003	0.242	0.235	0.267	0.256	-0.4	-0.4	-0.39	-0.4
11	All Weak, Combo Additive	450	208	233	235	373	1499	0.07/ 0.095	0.071/ 0.064	0.073/ 0.066	0.341/ 0.035	0.423/ 0.004	0.134	0.12	0.125	0.621	-0.15	-0.12	-0.11	-0.29
12	All Expected, Combo Additive	451	174	205	211	458	1500	0.141/ 0.041	0.212/ 0.030	0.221/ 0.024	0.839/ 0.010	0.903/ 0.002	0.046	0.044	0.058	0.852	-0.31	-0.24	-0.23	-0.69
13	All Strong, Combo Additive	450	153	183	195	518	1500	0.197/ 0.031	0.374/ 0.019	0.398/ 0.015	0.954/ 0.006	0.989/ 0.003	0.024	0.024	0.031	0.921	-0.47	-0.36	-0.35	-1.23