**Warning: Save your work at least every 15 minutes by clicking "Save" or "Continue."**

## Study Summary - Research Study

**1.0**

**Study Materials: As applicable to this study, attach the following:**

- **Protocol, Dissertation Proposal or Study Plan**
- **Preliminary Data**
- **Surveys, Questionnaires or other instruments to be used with study participants**
- **References**

| Document Name | Document Version # |
|---|---|
| Letter to PHFP UCLA 4_17_12 | 0.06 |
| Pt Survey 7 Day Paper Version – 9-26-11 | 0.01 |
| Equipment Return completed 4_17_12 | 0.02 |
| Pt Survey Baseline PAPER Version -- 9-27-11 | 0.01 |
| advisory group discussion prompts | 0.01 |
| Binder for Control Pts 4_17_12 | 0.04 |
| Equipment set up diagram 2_28_12 | 0.01 |
| Pt Survey 30 Day Paper Version – 9-26-11 | 0.01 |
| survey letter without gift card | 0.02 |
| Equipment Return Deceased 4_17_12 | 0.04 |
| Pt Study Brochure 4_17_12 | 0.01 |
| Call parameters revised -- 9-26-11 | 0.01 |
| Intervention Process Flow | 0.01 |
| Call parameters | 0.01 |
| Pt Survey 30 Day CLEAN 12_9_11 | 0.02 |
| Equipment Return TM Withdrawal 4_17_12 | 0.02 |
| Binder for Intervention Pts 4_17_12 | 0.04 |
| HF Education – 10-5-11 | 0.01 |
| Letter for locating unreachable patients | 0.02 |
| Description of Draft Survey Domains Sept 2010 | 0.02 |
| Pt Survey 180 Day Paper Version 7_24_13 | 0.02 |
| Letter to PHFP nonUCLA 4_17_12 | 0.04 |
| TIBI questionnaire – full version | 0.01 |
| Pt Survey 7 day CLEAN 12_9_11 | 0.03 |
| Equipment Return withdrawal 4_17_12 | 0.02 |
| Equipment set up diagram cell pod 3_19_12 | 0.01 |
| Call Parameters – 10-5-11 | 0.01 |
| PT Survey 180 Day 7_24_13 | 0.02 |
| Heart Failure Education Materials – Revised 9-27-11 | 0.01 |
| survey letter with gift card | 0.02 |
| TIBI – 10-5-11 | 0.02 |
| TIBI – 9-26-11 | 0.01 |
| Pt Survey 30 day TRK CHGS 12_9_11 | 0.01 |
| REALM-R Patient Word List for Baseline Survey | 0.01 |
| Call Parameters Table 10_27_11 | 0.01 |
| abbreviated 180 day survey | 0.02 |
| final gift card letter | 0.01 |
| Pt Survey Baseline CLEAN -- 9-26-11 | 0.03 |
| Heart Failure Education Materials | 0.01 |

**2.0** ***Specific Aims: Indicate the purpose of the research, specifying the problems and/or hypotheses to be addressed.**

1. Compare the effect of implementing the care transition intervention with concurrent controls on variation in readmissions

among elderly patients hospitalized with heart failure at the six medical centers.

2. Examine the change in variation over time in readmissions and mortality among hospitalized Medicare beneficiaries with heart failure at the six medical centers.

3. Compare the health benefits and costs of the care transition intervention.

**3.0** ***Background and Significance: Provide a summary of the background for this study and explain how it will contribute to existing knowledge.**

**For greater than minimal risk biomedical studies, include preliminary data. If necessary, attach in Item 1.0 graphs or tables used to convey information. If there no preliminary data are available, briefly indicate why this proposed study is a reasonable starting point.**

Recent studies by the Dartmouth Atlas of Health Care have identified geographic variation in hospital resource use and cost at the end of life among elderly Medicare beneficiaries with chronic illnesses. Reduction of variation in resource use and cost is a key focus for saving costs in the U.S. health care system. One potential area of intervention to reduce hospital resource use and cost variation is readmission rates, and interventions designed to improve the care transition period after hospital discharge have been shown to reduce readmissions and potentially improve morbidity and mortality at the patient level. However, no studies have demonstrated if care transition interventions would result in reductions in variation between hospitals on resource use or health outcomes. In addition, interventions that improve care transitions may be cost-effective at a societal level, but have not been widely disseminated due to implementation costs at the hospital level.

This comparative effectiveness project builds on our prior work examining variation in resource use and mortality among the five University of California Medical Centers plus Cedars-Sinai Medical Center for elderly Medicare beneficiaries hospitalized with heart failure. This work will begin to bridge the current gap between quality improvement research and studies of variation in care, and also provide an opportunity to compare the effectiveness of an existing care transition intervention with an approach that utilizes new technologies. Current studies of variation rarely have the clinical or organizational data to suggest ways to reduce variation between sites, and quality improvement work is often focused on changes at the patient or specific institutional level but not across institutions. Although care transition interventions are effective, they have yet to be widely disseminated due to their costs; telemedicine and centralized telephonic interventions that can be simultaneously implemented across a heterogeneous set of hospitals hold promise for potentially reducing these costs.

**4.0** ***Research Design and Methods: Describe in detail the design and methodology of the study.**

Each day during the intervention period, patients admitted as an inpatient or for observation at each site will be assessed by the project manager and the medical center study nurse for potential enrollment into the study. The project manager at each medical center will obtain information on these patients from the prior day, including their age and diagnoses on admission. Preliminary lists of potential HF patients will be developed based on the diagnoses on admission, including HF as well as other presenting symptoms consistent with HF (e.g., dyspnea, fatigue, edema) or being evaluated for conditions that may precipitate hospitalization for HF (e.g., atrial fibrillation). The patient identifier information (medical record number, name, birthdate) will be compared with study records to determine if the patient has been previously approached about participating in the study; and, if so, the patient will be excluded from the list of study candidates. For the remaining potential HF patients, the study nurse will then confirm with patients' attending physicians whether the patient, particularly for those only with presenting symptoms or precipitating conditions, should be considered as being actively treated for HF. In addition, the study nurse will determine from patient charts and/or dicussion with the attending physician if the patient should be excluded for any of the following reasons: patients with valvular disorders requiring surgical intervention (except for those with incidental valvular disease, who will be included), acute myocardial infarction (except for those with demand ischemia, who will be included), percutaneous coronary intervention (PCI), expected to enroll in hospice or expire after discharge.

The medical center study nurse will review the admission note for those individuals whose are being actively treated for HF, for exclusion criteria. Patients being admitted from a skilled nursing facility will be excluded from the study. For transplant patients, this is determined by checking the past medical history for receipt of a transplant, if the admission note states the patient is being admitted for transplant evaluation, or if the patient is on the waiting list for a transplant at one of the six study medical centers. The admission note will also be checked for information indicating the patient has dementia. Patients being admitted from or discharged to a long-term skilled nursing facility stay will be excluded. If the patient does not meet any of these exclusion criteria, the patient (or if the patient is unable to do so, the patient's decision maker) will be approached to determine if they should be excluded from the study based on subsequent criteria: chronic dialysis; lack of a working landline or reliable cell service; inability to use the intervention weight scale or otherwise unable to use the intervention equipment; inability to identify a usual source of care (free clinic is acceptable) and no provider being assigned upon discharge; or dementia.

At this point, eligible patients will be informed about the study. The study nurse will perform the evaluation of consentability with the patient using an online version of the Evaluation to sign a Consent form contained within our online screening and enrollment system, PIWeb, and will log the patient's responses into this online system. If the patient is deemed able to consent, then consent will be requested and the enrollment process will continue using PIWeb. As part of the consent process, we will inform the patient that if they provide us with a secondary contact, we will only contact this person at the phone number provided by the patient and only if we are unable to reach the patient after five attempts over three days. We will also inform the patient

that if we do contact the secondary contact, only the patient's name, that the patient is enrolled in our study, and that we have been unable to reach the patient in the specified time period will be disclosed. The secondary contact information will be entered into our online patient enrollment system and stored in our secure BEAT-HF data repository, along with all the other data collected on and from the patient during hospitalization, as described in our data security plan in section 9.3, subsection 2.1.

Once consent is obtained, the study nurse will administer the baseline survey and TIBI and enter the patient responses into our online survey system. Once the baseline survey and TIBI are completed, the patients will be randomly assigned using a web-based computerized random number generator to either the intervention group or the concurrent control group. A copy of the informed consent and HIPAA authorization will be placed in the patient's medical record.

For patients being evaluated for PCI, enrollment activities will proceed up through survey and TIBI completion, but randomization will only occur if the patient is determined to not require PCI. If the patient is determined to require PCI, then the patient will be ineligible for the study. The patient will be informed when approached that if a PCI is required, they will not be eligible for the study.

As randomization occurs upon enrollment, we can prevent those patients randomized to usual care from receiving additional services from the site study nurse provided to the patients in the intervention arm. Upon discharge, usual care control patients will only be contacted by the survey team and will not receive any calls from the centralized call center.

Intervention Arm Protocol Prior to Discharge: The study nurse at each site will work with each patient following enrollment and conduct the following activities:

1. Educate the patient about his or her HF condition, and key lifestyle measure using teach back approaches.
2. Educate patient regarding medications (e.g., explain what medications to take, review each medication's purpose, important side effects to watch out for, be sure patient has a realistic plan about how to get the medications) using teach back approaches.
3. Review the post-discharge protocol (see below).
4. Review the appropriate steps for what to do if a problem arises (e.g., a specific plan of how to contact the primary care provider (or coverage); discuss what constitutes an emergency and what to do in cases of emergency).
5. Educate the patients on use of the wireless remote monitoring device. The wireless remote monitoring component uses: a) a wireless weight scale and BP cuff for data retrieval, a communication device for data transmission and feedback from the research nurse, and a central data base for storage of all health data transmitted through the wireless interface. Patients will receive prior to discharge the biometric remote sensor devices (weight scale and a BP cuff to measure BP and heart rate), and the communication device, unless they ask for these to be mailed home. Study nurses will instruct patients prior to discharge on how to use the weight scales and BP cuff, and teach the patient on how to use the communication device (i.e. data transmission, text message receipt and sending). Patients and/or caregivers will be asked to demonstrate proficiency with using the equipment prior to discharge. Patients will be given a toll free number to report any technical problems and obtain technical assistance as needed.
6. Work with the patient to encourage attendance at post-discharge appointments for clinician follow-up (e.g., elicit input from the patient on the best time and date of the appointment; be sure the patient understands the importance of such services; confirm the patient knows where to go and has a plan about how to get to an appointment; review transportation options and other barriers to keeping these appointments).

Intervention Arm Post-Discharge Protocol: The intervention uses a centralized call center to contact the patient within 3 days of discharge to reinforce the discharge plan by using a scripted interview and to conduct problem-solving if necessary. Patients will be told to expect a follow-up call within 3 days of discharge. Instead of using the same nurses who worked with the patient in the hospital, this will be conducted by a centralized call center staffed by up to four study nurses. The centralized call center will have access to the hospital discharge summary, additional communications sent by the medical center's study nurse (e.g., non-English speaker, other involved caregivers), and each medical center's electronic medical records via remote access. The call center nurses will ask patients to bring their medications to the telephone to review them and address medication-related problems; at the first follow-up call the call center nurse will also assess any potential problems with care transitions. Any identified issues, medication or otherwise, will be relayed by pager and email to the primary HF provider, or if different, the primary care provider or provider who will first see the patient following contact. The primary HF provider will be notified about the patient enrollment in the intervention arm of the study by email or letter so that they will be aware of potential contact. If the patient is having trouble scheduling timely outpatient care, the call center nurses will assist with getting an appointment with the outpatient provider who is the primary HF provider. Patients will subsequently be called at a minimum on a weekly basis for a total of at least four telephone contacts during a 30-day period. However, call center nurses may increase the total number of calls during the 30-day period as deemed necessary. After the 30-day period, call center nurses will contact the patients on a monthly basis up through six months after discharge. These monthly calls will not be as intensive (e.g., will not explicitly go through each medication as described earlier) as the calls during the first 30-days period, but will be problem-oriented and will provide guidance on any HF management issues raised by the patient and/or caregivers.

Following discharge, patients will be asked to transmit automated biometric information and symptoms daily to the centralized call center using the communication device. Patients will be instructed to turn on communication device upon waking up in the morning and to turn it off before they sleep at night. As soon as the patient's personal communication device is switched on, it will remind the patient to perform their daily "Health Check" (e.g. obtain daily weight and vital signs). After their weight and vital signs are recorded in the system, patients will be prompted to respond to a series of symptom questions related to their HF status and general health. Information from the remote monitoring system will be automatically downloaded daily to a secure Internet site for review by the centralized call center nurses, with individuals flagged who have "variance triggers" from daily symptom reports or biometric data that are outside specified parameters (such as a weight gain of greater than 3 pounds in one day or 5 pounds in one week).

At the end of six months, patients will be asked to return the study equipment to the medical center using preaddressed packaging with prepaid postage that will sent to them at this time. For patients who choose to fully withdraw from the study or from the telemonitoring portion of the study prior to the end of their six month study period, shipping materials will be sent to the patient as soon as we are made aware of the withdrawal. For patients who expire during their six month study period, the patient's secondary contact will be contacted to determine the best mailing address and name for us to send the shipping materials. For patients we are no longer able to reach (i.e., provided phone numbers are no longer working or never answered), and from whom we would like to try to receive back study equipment, a letter will be sent ("Letter for locating unreachable patients") to the last known address we have for the patient, requesting the patient contact us either via telephone or using an enclosed, stamped and addressed envelope, to let us know how we can reach them. For patients who we are still able to reach, but who have for some reason not sent back the study equipment to us after receiving the prepaid return shipping materials, we will follow up with a phone call 10 days after the materials return package has been delivered to the patient, and offer two alternative means for equipment return: a study team member can pick up the equipment from the patient's home, or the patient can return the equipment at their next clinic visit.

Intervention Evaluation Survey: Intervention and control patients will be evaluated on admission and over the six months following discharge by survey. Each patient will be contacted by telephone within 7 days, 30 days and at 180 days post discharge by our survey research staff. Patients will receive a paper version of the survey as a guide for the follow up survey calls if needed. Patients who have completed the previous survey will receive a $10 gift card along with the paper version of the upcoming survey. Patients will receive a $10 gift card for completion of the final, 180 days, survey in the mail upon completion of the final survey. For patients who are not reached during the 4 week contact window for the 180 day survey, we will continue to try to reach these patients to have them complete an abbreviated 180 day survey. The abbreviated survey will also be offered to patients who are reached during the 180 day contact window, but who indicate they do not want to complete the full 180 day survey when contacted. Patients who a) received gift cards that had erroneously not been activiated prior to the cards being provided to our study team and then b) tried to use the cards at Target and were refused, we receive an additional $10 gift card in consideration for this issue.

In January 2013, we plan on holding the first of possibly two patient advisory council meetings. These meetings will consist of 3-5 intervention patients from each of the six institutions meeting at their enrollment institution to provide feedback on their experience at the hospital and with intervention program, which will help us shape future patient programs. The patients will meet as a group with a moderator, most likely the local project director, to participate in an open discussion that will include general topics such as: "overall did you find the program beneficial?", “what should we be doing going forward to best help you with managing your heart failure condition?”, "can you think of anything that you feel would have improved the program?", "what were the most positive and negative aspects of the program?", "would you be willing to participate in this type of program again?". For patients who would like to share their thoughts on the program with us, but who are unable to physically make it into our offices to attend the group session, we will offer them the option of providing feedback by telephone interview, answering the pt advisory group questions privately, over the phone, instead. In addition, for patients who would would like to share their thoughts on the program with us, but for whom a group meeting cannot be arranged, we will offer them the option of answering the pt advisory group questions during their next clinic visit.

In addition, in order to obtain complete and accurate information about patient hospital stays during the study period, we need to share patient SSNs with the California OSHPD. OSHPD collects information on all hospitalizations from hospitals in California, including SSN; so will provide SSNs again to OSHPD to ensure the most accurate match between our study records and OSHPD’s records.

**4.1** * **Will you be providing results of any experimental tests that are performed for the study?**

- ○ Yes - Complete Items 4.1.1 and 4.1.2
- ○ No
- ◉ Not Applicable

**4.1.1** **You indicated in Item 4.1 that the research involves experimental tests. Please describe the tests, provide a rationale for providing participants with the experimental test results and explain what, how and by whom participants and their health care provider will be told about the meaning, reliability, and applicability of the test results for health care decisions.**

**4.1.2** **Will tests be performed by a Clinical Laboratory Improvement Amendments (CLIA) approved lab?**

○ Yes ○ No

**5.0** ***Indicate how much time will be required of the subjects, per visit or contact, and in total for the**

**study.**

All individuals will be surveyed within 7 days, 30 days, and 180 days after discharge by telephone; we anticipate one hour for each contact.

We expect that individuals randomized to the intervention group will spend several hours with the discharge protocol prior to discharge, and they will receive at least four telephone contacts during the first month after discharge, with monthly telephone contacts for the subsequent five months. In addition, patients in the intervention arm will be asked to transmit information daily through the six month period after discharge and called on an as-needed basis by call center nurses if variance triggers are detected. These contacts will vary based on the clinical state of the patient.

Patients who have agreed to be contacted for additional studies and consent for continued tracking of utilization and outcomes through 365 days after discharge will be asked to transmit information daily through the six month period after the initial 180-day period and called on an as-needed basis by call center nurses or similar providers if variance triggers are detected. These contacts will vary based on the clinical state of the patient. These patients will also be surveyed after 365 days after discharge by telephone; we anticipate one hour for this contact.

6.0 ***Statistics and Data Analysis: Describe the proposed statistical procedures or descriptive analyses for the study. If applicable, indicate how the sample size was determined.**

Our analytic approach uses multivariate regression analysis to predict study outcomes for each of the six medical centers, adjusted for differences in patient characteristics that can influence resource use and mortality. The primary goal in this randomized trial is to estimate the difference in effects on outcomes between the pre-intervention group and the intervention group. These analyses use an intent-to-treat (ITT) framework, within a hierarchical approach using information on medical centers and patients. We will apply multi-level models (also known as hierarchical models or random coefficient models) to account for the multilevel data structure, with two-level models for analyses of patients nested within medical centers, and three-level models for analyses of repeated measurements for patients nested within medical centers. We refer reviewers to the federal grant application's "Statistical Analysis Plan" for more details regarding the statistical procedures and analyses.

Based on our analyses of our prior data from 2007 and 2008 and accounting for the listed exclusion criteria (with the exception of the working phone which we cannot ascertain), we expect approximately 1740 patients that will meet study criteria to be admitted within the 18 month intervention period; with a refusal rate of approximately 15% we expect an enrolled sample of 1500 patients.

findings for the effectiveness measures; if the intervention does not lead to improved outcomes (or a full cost-offset), a more limited set of analyses will instead be performed to describe the costs and correlates of care for the study population.

The marginal cost-effectiveness of the intervention is the estimated difference in cost incurred by the intervention group (in our case, relative to group receiving "care as usual") divided by the estimated difference in effectiveness. Our primary effectiveness measure is prevented readmission, although we will also evaluate other measures of effectiveness, e.g., quality-adjusted life year using mortality and EQ-5D data:

$$\frac{\text{marginal cost}}{\text{readmission}} = \frac{\text{Difference in costs between the two intervention groups}}{\text{Difference in readmission rates between the two intervention groups}}$$

**Statistical Analyses Plan**

General Framework: Our analytic approach uses multivariate regression analysis to predict study outcomes for each of the six medical centers, adjusted for differences in patient characteristics that can influence resource use and mortality. These regression analyses will follow the general form of

$O = f(H, C, X, Y)$, where

- $O$ = Outcome
- $H$ = Hospital site variable
- $C$ = a vector of explanatory variables of interest
- $X$ = a vector of patient sociodemographic factors
- $Y$ = a vector of patient comorbidities

To improve the precision of the estimated intervention effect, we will conduct a series of bivariate analyses to identify the potential covariates to be considered for a multiple regression model. Confounding will be assessed by comparing the unadjusted coefficient for treatment condition with the adjusted coefficient. We will use model-building strategies to obtain final models.[57] Assumptions of normality will also be evaluated. For example, we will explore various transformations (e.g., log and square root) for life event variables due to the often skewed distribution of event counts. Smearing estimates will be used, if necessary, for retransformation, applying separate factors for each intervention group to ensure consistent estimates.[58-60] In general, we leave open the possibility of transforming variables with non-normal distributions.[61]

Due to the resource use-based study inclusion criteria, hospital days and total costs should always be positive, and their distributions are likely to be very skewed. Other outcomes of interest will also have a very skewed distribution, either because there will be many zeros (e.g. ICU use) and/or because the distribution of observed values has a very long tail (e.g. total ICU days). In such cases, we will draw upon statistical models developed for handling these type of data, such as two-part models to separately handle zero values and a skewed distribution among non-zeros,[58-60] Tobit-type sample selection models;[62] split-sample techniques to distinguish between different functional forms and to avoid overfitting;[58-60] and dynamic models, such as episodes of care analytic models, duration analysis, and count models (e.g., Poisson and negative binomial models).[63, 64] The initial models for each outcome will be the same as prior work by our group in order for comparability.[22] We will initially use zero-truncated Poisson regression models for total hospital days, zero-truncated negative binomial regression models for total hospital costs and logistic regression models for readmission and mortality. In these cases, zero-truncated Poisson or zero-truncated negative binomial models are needed to account for the non-zero distribution of resource use. We will confirm model selection with goodness of fit tests. We use the Huber-White sandwich estimator to obtain robust standard errors for the regression coefficients that accounted for the nonindependence (i.e., clustering) of observations within medical centers.

Hypothesis 1 Analyses: The primary goal in this randomized trial is to estimate the difference in effects on outcomes between the pre-intervention group and each intervention group, and between the two intervention arms (e.g., telephone vs. telemedicine approaches). These analyses use an intent-to-treat (ITT) framework, within a hierarchical approach using information on medical centers and patients. We will apply multi-level

models (also known as hierarchical models or random coefficient models) to account for the multilevel data structure, with two-level models for analyses of patients nested within medical centers, and three-level models for analyses of repeated measurements for patients nested within medical centers.[65-68]

*Two-level model for cross-sectional data analysis*: The statistical model for a "cross-sectional" analysis with one observation per patient is presented via two regression equations:
Level 1 (patient): $Y_{ij} = b_{0j} + b_{1j}X_{ij} + e_{ij}$ $e_{ij} \sim N(0, s^2)$,
Level 2 (medical centers): $b_{0j} = r_{00} + r_{01}V_j + r_{02}W_j + u_{0j}$ $u_{0j} \sim N(0, T\square)$,
where $Y_{ij}$ denotes the outcome for the i-th patient in the j-th medical center, i=1, …, $n_j$, j=1, …, J; $X_{ij}$ denotes a vector of covariates at the patient level; $V_j$ denotes treatment status for the jth medical center; and $W_j$ denotes a vector of predictors at the medical center level. These two equations can be presented in the mixed model:
$Y_{ij} = r_{00} + b_{1j}X_{ij} + r_{01}V_j + r_{02}W_j + u_{0j} + e_{ij}$ $e_{ij} \sim N(0, s^2)$, $u_{0j} \sim N(0, T)\square$.
The random intercept model can be generalized to a random intercept, random slope mode that also specifies $b_{1j}$ to be random with a multivariate regression for $(b_{0j}, b_{1j})^T$ at Level 2. For binary outcomes, we will use generalized linear mixed models that use a binomial model and a logit link function at Level 1.

*Three-level model for longitudinal data analysis*: The statistical models for a group-level randomized trial with repeated measures on patients can be presented via a growth curve model for the trajectory of the outcome measure over time with three regression equations:
Level 1 (Observation level, repeated measurements within patients):
(1) $Y_{mij} = b_{0ij} + b_{1ij}T_{mij} + e_{mij}$
Level 2 (patients):
(2.1) $b_{0ij} = C_{00j} + C_{01j}X_{ij} + r_{0ij}$
(2.2) $b_{1ij} = C_{10j} + C_{11j}X_{ij} + r_{1ij}$
Level 3 (medical centers):
(3.1) $C_{00j} = d_{000} + d_{001}V_j + d_{002}W_j + u_{00j}$
(3.2) $C_{10j} = d_{100} + d_{101}V_j + d_{102}W_j + u_{10j}$
where $Y_{mij}$ denotes the outcome at the m-th occasion for the i-th patient in the j-th medical center, m=1, … $t_{ij}$, i=1, …, $n_j$, j=1, …, J; $T_{mij}$ denotes time relative to baseline, $V_j$ denotes the intervention indicator, $X_{ij}$ denotes vector of other covariates at patient level, and $W_j$ denotes vector of predictors at the medical center level. Our analysis will be focused on the slope coefficient $d_{101}$ that measures the main effect of treatment on the growth rates. Specification of the covariance structure among the random effects will be modeled allowing for covariance between random intercepts and slopes. [69, 70] Given three repeated measures on patients and reasonable smoothness assumptions, we will explore curvilinearity through non-linear terms, e.g. quadratic terms, allowing insight into whether changes are greater in the earlier or subsequent periods.

Hypothesis 2 analyses: These analyses use the hospital as the unit of analysis, and will combine study participants from all arms of the trial. We will predict study outcomes for each study medical center during the 18-month period under three different scenarios that simulate a hypothetical situation where all study participants enter one of the three study arms. The regression analyses will differ from Hypothesis 1 analyses in two ways. First, we will use the medical centers as a fixed categorical variable (with one serving as the reference group), as opposed to a random variable in Hypothesis 1 analyses. Second, we will include a categorical variable with three levels to separately represent the two interventions and the control group. The coefficient for this variable will be used to predict scenarios for the intervention period in the recycled predictions, where we will set either all individuals to the hypothetical situation of receiving the telemedicine intervention (e.g., values for the telemedicine group set to 2, telephone group set to 1, control group set to 0). We will also conduct interaction analyses between the variables representing the medical centers and the interventions. Recycled predictions will be used to estimate study outcomes at each study medical center by simulating a situation where the medical center treats the entire study population.[71-76] This method minimizes the likelihood of selection bias of patients affecting results. We use the delta method to obtain standard errors for each hospital's risk-adjusted means and proportions and to conduct statistical tests of pair-wise differences between hospitals in these outcomes.[77-79] To ensure that standard errors and tests account for clustering, we will apply the delta method to the robust variance-covariance matrix estimates obtained using the Huber-White estimator. For each outcome, we will then use the range of predicted values for each medical center under the

three scenarios (all receive the telemedicine intervention, all receive the telephone intervention, all receive no intervention), and determine the amount of variation among all sites by examining the range of predictions. We will then conduct significance testing on the ranges of predictions under the three scenarios for each outcome.

Hypothesis 3 analyses: These analyses will be similar to those used for Hypotheses 1 and 2. We will include variables representing the mediating care transition measures and total number of outpatient visits, and evaluate the independent effect that each variable has on study outcomes.

Hypothesis 4 Analyses: These analyses mirror the analyses conducted for the Acting to Reduce Variation in Utilization project except that we predict outcomes for patients with initial hospitalizations during 2006-2010.[22] We will then compare changes between analyses conducted with data from 2001-2005 and 2006-2010.

Hypothesis 5 analyses: The analysis of the difference in use and costs between the intervention and control groups, and the two intervention groups, will proceed in a fashion similar to that for the other endpoints, i.e. costs at follow-up will be estimated as a function of baseline costs and other covariates shown to be unbalanced between the two groups. Due to the skewed distributions typical for cost measures, we will perform transformations of the dependent variable and appropriate retransformation algorithms.[59, 80, 81] Hospital days will be estimated using negative binomial models. Two-part models may be required for limited-dependent variables with large numbers of zero values, e.g., health care costs. Non-parametric bootstrapping methods will be used to derive standard errors and confidence intervals around the C/E ratios, by drawing random samples with replacement from the two intervention groups and computing the variance of a large number of replications of the incremental C/E ratios.[82]

To calculate the "predictive margins," the value of the intervention indicator will be set equal to one for all patients and, holding all other regressors at their reported values, the predicted value of costs will be calculated for each patient. The intervention indicator will be reset to equal zero, and predicted costs will be recalculated, again keeping all other regressors at their reported values. The sample average of the differences between the two predictions thus obtained will be computed, along with bias-corrected, empirical 95% confidence intervals derived using non-parametric bootstrapping methods.

We will then generate a Markov chain model and conduct simulations using predicted rates of events, associated costs, and values to generate point estimates and 95% confidence intervals for cost-effectiveness ratios. We will then conduct one-way and probabilistic sensitivity analyses to determine conditions for meeting typical thresholds of cost-effectiveness.

In addition to the cost-offset and cost-effectiveness analyses, we will conduct cost-utility analyses with utility data from the EQ-5D questionnaire administered at each assessment. The advantage of using preference-based health-related quality of life ("utility score") measures of effectiveness is that it permits comparison of the cost-effectiveness of these interventions with other interventions in diseases with disparate clinical endpoints.[83] The KCCF will not be used for cost-effectiveness analyses, but for reporting HF-specific outcomes.[35, 84]

Power Calculations: For power calculations regarding our Aim 1 interventions, we assume that the control group will have readmission rates similar to the unadjusted mean rates for 30-day (16.3%) and 180-day (38.0%) readmissions from 2005-2008, a significance level of 0.05 and a power level of 0.80. For analyses comparing each intervention with controls (each group n = 500); a significant change in 30-day readmissions would be from 16.3% to 10.3% (a 36.9% relative change) and in 180-day readmissions from 38.0% to 30.7% (a 22.0% relative change). These are relatively the same effect sizes as seen with the Transition Coach model, which showed a 30.3% relative change in 30-day readmissions and a 16.6% relative change in 180-day readmissions;[15] greater changes have been seen in telemedicine trials.[85] As this is an effectiveness trial, we may expect lower effect sizes than seen in efficacy trials. However, the telephone intervention extends contact beyond the Transition Coach model of 30 days to 180 days; longer interventions have been shown to have greater effects.[13, 14] Comparing the telephone and telemedicine intervention on readmission effects will require similar effect sizes as all groups are projected to have the same sample size. We do not expect to detect a significant difference between the two interventions on readmissions; we do expect differences in the cost of

the interventions, which for the telephone intervention is essentially costs associated with the centralized call center, and for the telemedicine intervention are the fixed cost of the devices plus hypothesized lower use of the centralized call center. If the telemedicine intervention uses less than 15% of the centralized call center effort, we estimate the average cost per telephone patient will be over $500 (we assume the pre-discharge activities will be incorporated into standard discharge planning services). Assuming a standard deviation of $50, a significance level of 0.05, and a power level of 0.80, we should be able to detect a significant difference in mean costs of $9; we estimate the average cost per telemedicine patient to be under $490 with less than 15% effort (and vice versa with over 16% effort).

For Aim 2 analysis power calculations, we assume a sample size of approximately 4600 patients for 2006-2010 and 4000 patients for 2001-2005. The 2001-2005 cohort predicted readmission rates at 30-days was 17.3% and at 180-days was 40.9%. We will be able to detect at a significance level of 0.05 and a power level of 0.80, a reduction in readmission rates at 30-days down to 15.1% and at 180-days down to 38.0%.

Missing Data: Missing data can result in response bias. It is known that mixed-effects models handle cases with incomplete follow-up based on an implicit missing-at-random assumption.[86] If there are variables that are not included in the mixed-effects model but are relevant to the missing data mechanism, a model without those variables may lead to biased estimates. In addition, many software programs for mixed-effect models drop participants from analyses when any explanatory variable is missing. We will use multiple imputation techniques to account for missing data and the uncertainty in the imputed values.[86-88] The analytic team has extensive experience with multiple imputation.[89-92] Due to the sensitivity of inferences to underlying data distributions,[92] we will consider hot-deck and model-based imputation, relying on hot-deck strategies when data distributions are highly skewed but leaving open the possibility of handling several variables simultaneously using model-based strategies if data distributions appear suitably behaved.

Multiple Comparisons: We will consider but will not rely solely on Bonferroni adjustments and related methods that incorporate bounds on the probability of a single false finding of significance.[93] We will also consider the false discovery rate (FDR),[94] a framework that offers more sensitive tests of significance when large numbers of tests are carried out by comparing observed significance findings with expected order statistics from a uniform distribution.

Subgroup Analyses: Although we are not powered to identify a similar effect on priority populations, such as patients whose racial/ethnic background are Hispanic/Latino, Black, or Asian, we will conduct analyses that focus specifically on these populations in order to generate future hypotheses that can be explored with an expanded study powered to examine effects in these priority populations. We will also conduct subgroup analyses based on the type of HF, whether systolic or diastolic HF.

**Management**

The study will be managed by the PI and Co-PI (Ong and Mangione), supported by an Executive Committee. Each medical center will designate one representative from its investigator group to participate in an Executive Committee. The Executive Committee, with input from key stakeholders, will vote on decisions regarding necessary decision regarding the data collection, study progress, analyses, and dissemination. Decisions require unanimous agreement among all medical center representatives on the Executive Committee. This same governance structure was used in both phases of the Acting to Reduce Variation in Utilization projects, such as to determine whether identities of the specific medical centers would be disclosed within the group and to the general public. The representatives from each medical center will conduct a monthly teleconference meeting to discuss issues regarding the consortium, and will also meet in person at the annual meetings of the investigators with key stakeholders.

**Limitations**

Some health care resource use will occur in settings that cannot be identified in data systems for the six medical centers. Prior studies suggest very high “hospital loyalty” among patients hospitalized for chronic illnesses,[95] and found that chronically ill patients hospitalized in any of the six medical centers had 80-90% of their total hospital days at the same site.[2] However, to further mitigate this issue for our analyses, we collect