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Title: “Multicomponent Intervention to Prevent Delirium in Nursing Homes”

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A. SIGNIFICANCE

A.1 Importance of delirium in nursing home patients

Delirium is frequent and adversely affects quality of life in older adults. Approximately one third of older adults hospitalized with acute medical problems experience delirium.[1, 25-26] Delirium in nursing homes, as in hospital settings, is often precipitated by acute illness. Nursing home residents experience 2-4 acute illness episodes per year (e.g., respiratory, urinary tract, and gastrointestinal infections),[27-28] and ¾ of these are managed in the nursing home. Studies show a delirium prevalence of 16-23% at the time of nursing home admission[3-4] and up to 33% in nursing home long-term care,[5-6] and a nearly universal presence of multiple delirium risk factors (one or more of: cognitive impairment, immobility, sensory impairment, and neuropsychiatric medication use).[7-10] Delirium is reported to be an uncomfortable and traumatic experience by those who have experienced it – with acute distractibility, disorientation, hallucinations, and change in alertness – and for family witnesses.[29] In longitudinal studies of delirious nursing home patients these symptoms last for 1-9 weeks in those whose delirium remits, but 20% of delirious nursing home patients remain symptomatic past 24 weeks of follow-up.[30] Many nursing home patients who develop delirium do not return to their pre-delirium level of cognitive function.[11] Delirium in nursing home patients is a powerful risk factor for poor health outcomes. As compared to those without delirium, patients with delirium are more likely to die,[5] be hospitalized or rehospitalized,[12] and less likely to be discharged home.[12] These adverse outcomes parallel the outcomes of hospitalized older adults with delirium, who have longer hospital stays, 2-3 fold higher mortality at 1 year, and increased risk of nursing home stays.[31] Cognitive change indicative of delirium is a common reason for hospital transfer of nursing home patients.[13-14] The association of delirium with increased hospital use drives excess costs, with total 1-year excess costs attributable to delirium between $18,024 - $71,221 per patient in 2014 dollars.[15]

A.2 Lack of existing approaches to delirium in the long-term care setting

In contrast to hospital, intensive care, and peri-operative trials that have targeted delirium,[32] few studies exist of interventions to prevent or treat delirium in the long-term care setting. *Since the last submission, a Cochrane review[33] identified only 2 prevention trials: one small study (n=98) of a hydration-only intervention that showed no reduction in delirium,[34] and one of a medication reduction-only intervention that reduced administratively-ascertained potential delirium by 58% (HR 0.42, 95%CI 0.35-0.52).[35] Among the few nursing home delirium treatment trials, a multi-factorial intervention that was designed to be delivered by existing nursing home staff to delirious post-acute nursing home patients was not effective in shortening delirium or reducing its severity, in part because of a lack of staff adherence.[36] Some new efforts are underway: an education and practice change package that has been shown to increase nurses' confidence in delirium recognition and management is currently undergoing multi-site pilot-testing,[17, 37] and intervention workflow design work is being done by other investigators.[38-39]* As a result of the relative research void in this area, we developed an intervention for nursing home patients, adapted from the Hospital Elder Life Program (HELP) [19, 40] and with input from multidisciplinary nursing home expert stakeholders, that delivers delirium-risk-abating components via a mobile geriatrics care team that includes an Elder Life Specialist (in our case a trained certified nursing assistant (CNA)), supported by a geriatrician, working in collaboration with the patient's primary medical and nursing team. We demonstrated the feasibility of implementing the intervention at the onset of acute illness, and showed favorable acceptance by patients and staff over 1 year at an urban nursing home.[20] The current application proposes to test the efficacy of this intervention in a single-site cluster-randomized trial.

A.3 Importance of nursing homes as sites of care for U.S. older adults

There are more than 15,000 nursing facilities in the United States with approximately 1.4 million patients, constituting 17.5% of persons older than 75.[7] A 50-year old American has a 53–59% lifetime likelihood of admission to a nursing home and if admitted, the average lifetime number of days spent there is 370.[41] Nine percent of hospital discharges are to nursing facilities[42] and, as hospital stays have shortened, nursing facilities are caring for patients with greater complexity and instability. The Centers for Medicare and Medicaid (CMS) recognizes the importance of nursing home care in its efforts to improve care for older adults, with publicly reported nursing home quality measures,[43] CMS innovation awards to reduce avoidable hospitalizations among nursing facility residents, and a quality initiative ("QAPI") obligating nursing homes to develop and implement process improvements.[44] 2013 Medicare expenditures and 2011 Medicaid expenditures for nursing facility care were $29 billion[45] and $52 billion,[46] respectively. In this way, delirium prevention may not only to improve health, but also reduce hospitalization and costs, opening up potential for broad adoption.

B. INNOVATION

B.1 Framework: Acute illness as a delirium-precipitating event

The study framework is novel in its focus on nursing home residents with acute illness. The American Psychiatric Association Diagnostic and Statistical Manual defines delirium as caused by an acute medical problem (e.g., a new infection) or its management (e.g., a medication change),[47] and pathophysiologic studies point to neurotransmitter alterations caused by illness-associated inflammation, endothelial dysfunction, and

blood flow changes as possible causes of delirium.[48] This framework applies to acutely ill nursing home patients who share characteristics with hospitalized older adults that include acute illness diagnoses (e.g., respiratory, urinary, and gastrointestinal infections), age, comorbid conditions, immobility, and cognitive impairment. The PI has demonstrated the feasibility and reliability of enrolling nursing home patients with acute illness and collecting daily cognitive symptom information from them during treatment and after recovery.[18, 49] He has obtained IRB approvals to conduct research observations at the onset of acute illness in nursing home patients with patient assent, since such observations are minimal risk but require immediate implementation. The current proposed study builds on this procedural experience.

B.2 A short-term intervention in the nursing home with dedicated nursing assistant (CNA) staffing
The intervention is novel in that it provides structured nursing assistant visits to nursing home patients during a short period of high delirium-risk, namely during acute illness and for 1 week after recovery, as a supplement to (not replacement for) standard care. This approach addresses the difficulty of targeting delirium prevention efforts during a nursing home stay that can span weeks, months, or years. We chose HELP as a model for our intervention in part because studies show that setting-specific adaptations to the model can be made across multiple domains, including enrollment criteria, screening and assessment tools, and intervention protocols, while remaining effective.[50-52] *With input from medical and nursing long-term care experts, we adapted the HELP intervention to be delivered by a dedicated, mobile CNA, as opposed to existing nursing home staff , and instead of trained volunteers (as in HELP), whose availability is uncertain in nursing homes and with whom safety may be a concern working with very frail disabled older adults. CNAs are already integral care team members in the nursing home and have the skills to deliver intervention components with a small amount of additional training. A dedicated staff that is mobile between units also allows a shift in care intensity to nursing home patients when they need it -- i.e., when they develop an acute illness. In general, unit nursing staff, in a fixed staff-to patient ratio, cannot shift to provide the level of intervention intensity (1-2 visits daily, 30 minutes each) likely needed to prevent delirium.[19] Attention to other patients or tasks may be reduced. In addition, this role has precedence in the nursing home setting in such roles as CNA champions (e.g., oral care or falls specialists[53-54]) and rehabilitation or recreation therapists. We designed protocols to avoid inappropriate overlap with daily nursing activities by open communication between the intervention CNA and unit-based staff -- to tailor visits and ensure safety. Finally, although the CNA documents activities in the chart, s/he does not provide didactic or consultative advice. Our intervention also provides a potential career or training track for CNAs to gain specialized expertise that they bring to their unit or across units and an opportunity for promotion.*

B.3 Ascertaining delirium as a patient-centered outcome in patients with and without dementia. Our intervention provides an enhancement to direct care and we will measure its effect on outcomes important to nursing home patients and clinicians. This contrasts with nursing home initiatives whose sole focus is reducing hospitalization, with their difficult-to-predict patient health consequences.[55-56] We plan to include patients with dementia as long as they are verbal and can follow simple commands, since such patients make up half of nursing home patients,[21] are at high risk for delirium, and excluding them would limit the clinical relevance and applicability of our findings. In addition to using the Confusion Assessment Method[57] to classify delirium, we will use the Delirium Index,[58] an instrument that has been shown to be reliable in hospitalized patients with and without dementia, and has been used to characterize the course of delirium in the nursing home setting.

B.4 Preliminary studies. In addition to studies establishing our enrollment and assessment procedures,[18, 49] we have conducted preliminary studies to demonstrate the feasibility of intervention procedures and acceptance by nursing home staff.[20] *First, we developed standardized procedures and training (Appendix 2) in collaboration with a HELP Center of Excellence. At start up and thereafter we instituted a weekly whole-team rounds and discussion of each patient to optimize intervention fidelity.* In 2013 we implemented the intervention during 149 acute illness episodes at the study site, for a rate of 14 per month. 63% of patients were female, 37% Spanish-speaking, with average age of 83 years. The mean Brief Interview of Mental Status score was 7.5 (max possible score 15), indicating moderate cognitive impairment. The most common illnesses initiating receipt of the intervention were infections of bladder (29%), lower respiratory tract (18%), and skin (10%). Intervention CNAs delivered on average 14.2 visits over a 13.5 day span per episode, with average visit length of 30.5 minutes. Patient adherence to each of the components per visit ranged from 70-94% (Table 1), with a goal of 75%. The most common reasons for not receiving a component were patient refusal and patient off floor or unavailable. In a semi-structured interview of 28 patients who were capable of providing feedback, 27 had high satisfaction with the intervention and endorsed the value of each intervention component. *On days when 2 CNAs visited the same patient (n=179), percent agreement on provision of the key intervention components (orientation, mobility, fluids) was high, ranging from 80-93%, indicating excellent fidelity.* Among 4 physicians and 13 unit nursing staff who participated in a semi-structured interview, all indicated that communication between unit and intervention staff was effective and 14 endorsed that work stress was lower with the intervention, indicating good integration between intervention and unit nursing activities. *Staff*

indicated that they appreciated and recognized the intervention CNA as a mobile staff member who delivered focused services to patients on the floors, but not daily care. Delirium occurred during 22% of acute illnesses and 5% of patients were transferred to the hospital during or within 30 days after finishing the intervention.[20]

B.5 Investigative team

The PI has conducted innovative research to improve care in nursing homes, including interventions with CNAs, that has been widely cited and adopted.[28, 59-60] He has worked with nursing homes in New York and nationally to implement innovative models of care. Dr. Inouye (co-investigator) is the developer of HELP and the Confusion Assessment Method measure, and brings practical clinical trial experience.[19, 57] Dr. Teresi (Data Coordinating Center lead) has extensive experience in nursing home based research, measurement, and oversight of analyses from clinical studies.[61] Advisory group members have been selected who provide expertise in the areas of delirium (Hung), nursing home (Colon-Emeric), and long-term care nursing (Brody).

C. APPROACH

C.1 Overview. We propose to perform a controlled trial of a multicomponent intervention to prevent delirium at a large nursing home in New York City. The trial will be randomized by unit and evaluator-blinded. We will randomly assign 17 long-term care units to intervention or control and screen nursing home patients on each unit who experience onset of an acute change in condition according to established criteria and enroll 306. Those assigned to intervention (n=153) will receive daily visits from a mobile CNA trained to provide services to counter established risks for delirium, including dehydration, immobility, cognitive impairment, undernutrition, and sleep problems, for the duration of the acute illness and for 1 week following, in collaboration with the patient's primary medical and nursing team. Patients assigned to control (n=153) will receive usual care from the unit-based team. Delirium will be assessed 5 days a week by a research assistant (RA) blinded to study hypotheses and group assignment. Cognitive and physical function decline and hospital transfer will be ascertained during a 1 month follow-up period. We will conduct analyses to compare outcomes between intervention and control, as well as examine associations between outcomes and intervention features such as number and duration of visits. We will use regression models to adjust for covariates and effects of clustering.

C.2 Patient identification and enrollment. Patients on one of 17 long-term care units at Jewish Home Lifecare (JHL) in the Bronx will be screened for onset of acute change in condition by case-finding and referral, according to previously reported methods:[18, 49] an RA will review daily medical and nursing notes in the facility's electronic medical record for individuals with significant new symptoms or diagnosis requiring evaluation (e.g., labs), monitoring (e.g., vital signs), and/or treatment (e.g., antibiotics). In addition, the RA will accept telephone or in person referrals from unit-based medical and nursing staff who have been briefed on the requirements of the study. Nursing home patients returning from the hospital after an acute illness will also be screened. Patients will be enrolled who fulfill the definition of an acute change in condition as described by the American Medical Directors Association guideline[62] (Appendix 1), or who have been flagged by unit nurses for "24-hour report" meaning their acute change requires additional active monitoring by the unit team. *Change in condition criteria include symptom, vital sign, and exam findings that may be indicative of acute illness and are designed to be highly sensitive to assist nurses in triaging their alerts to medical providers. Patients on nurse's 24-hour report are those that nurses deem at risk and consequently receive additional nurse monitoring and documentation (e.g., not eating, after a fall, or with other new symptom).* Patients must also fulfill the following entry criteria: 1) anticipated nursing home stay of at least 2 months (i.e., not a short-stay, subacute patient, since subacute patients usually receive services that overlap with intervention components), 2) patient not receiving hospice care (since the intervention activities may not be consistent with the comfort care goals of hospice patients and might be burdensome), 3) patient passes a simple screen indicating he/she is verbal and able to follow simple commands (in order to be able to follow simple commands required to participate in intervention activities), and 4) patient and/or legal surrogate provides assent to participate. In our prior experience the frequency of exclusion of non-subacute patients by reason was: 3% hospice, 4% nonverbal, and 3% refusal. We have received JHL IRB approval for a modified consent process that allows patients and surrogates to assent to participate (as opposed to sign consent) because of the low risk of the intervention, the need to initiate the intervention immediately after a change in condition starts, and delays associated with obtaining written consent from patients or legal surrogates (see Human Subjects Section; IRB approval letter). *For this revision we collected pilot data to ascertain the sensitivity of our approach to identifying patients. Among 113 patients in 1 month who had a definite acute illness as defined as receiving IV or antibiotics or being sent to the hospital (gold standard), there was 1 patient who was not captured by change in condition criteria or 24-hour report, for a capture rate of 99.1% (95%CI 97.4-100). In 39 (34.5%) of cases, the change in condition preceded receipt of IV, antibiotics, or hospital transfer by a range of 1-11 days, which provides an opportunity to provide delirium risk reduction components before a definitive diagnosis or treatment begins.*

C.3 Assignment by unit. This is a cluster randomized trial; units will be assigned to intervention or usual care arms. This design will prevent a unit from having patients in both groups and the likelihood of contamination.

Prior to initiating study enrollment, a biostatistician from the Data Coordinating Center (DCC, at a separate location) will assign units to intervention or usual care using a SAS macro. Units are uniform (e.g., there are no specialized dementia units) except that 1) 1 unit has equipment and programs for visually impaired, and 2) some units are larger (38-42 beds) than others (34-35 beds). Thus, the randomization procedure will maintain approximate balance by randomly assigning 5 larger and 3 smaller units to one arm and 4 larger and 5 smaller units to the other. Each unit will keep its assignment for the duration of the study. With rolling enrollment and a planned sample size of 306 we anticipate enrolling approximately 18 patients per unit (mean cluster size = 18).

C.4 Intervention and control. Residents with acute illness on intervention units will be seen by an intervention CNA at least once daily 7 days a week. The CNA will be English/Spanish bilingual and will provide intervention components as shown in Table 1 guided by structured protocols and a daily visit form (Appendix 2). A typical visit lasts 30 minutes and begins with an introduction and orientation activity followed by provision of water, a reminiscence activity or game, a physical exercise, and a snack and second cup of water. Patients may also receive a relaxation visit at night and given a warm drink, a hand or foot massage, and quiet music. Daily visits will last for the duration of the illness and 7 days following the illness end. Illness end is defined as the last day of illness treatment (e.g., last day of antibiotics) or monitoring (e.g., last day on nursing "24-hour report"). Seven day a week coverage, provided by 1.4 FTE CNAs, is important for this intervention since it is a relatively brief (e.g., 2 week) intervention. Medication review using American Geriatrics Society Beers criteria[63] for drugs associated with delirium will be semi-automated and alerts provided to the primary team by secure messaging or telephone. During weekly intervention staff meetings patients in the intervention group will be discussed with the primary medical and nursing team. The planned intervention group sample size results in a caseload of 4-8 patients seen daily, which is well within the workload capacity of the intervention CNAs. Patients with acute illness on control units will be cared for as usual by the primary nursing home nursing and medical staff.

Table 1. Intervention components: all components delivered by the CNA except for medication alerts

Risk Factor	Intervention	Recipients / Tailoring	Evidence	Adherence*
Cognitive Impairment	1) Daily visit &orientation activity 2) Therapeutic activity: reminiscence, reading, music, pictures	All patients.	1) Cognitive impairment is delirium risk factor[8-10]	94% (79 off floor or unavailable; 23 refusals)
Immobility	Mobilization protocol performed to patient's maximum ability: 1) chair stands 2)walking 3) range of motion	All patients. Patient's maximum determined by intervention CNA from chart, patient and staff report, and observation	1) Early mobilization effective[19] 2) NH delirium assoc w/restraints[64] 3)Delirium assoc w/fall[65]	77% (382 refusals; 80 off floor or unavailable)
Dehydration	Hydration protocol: two 6-ounce cups of fluid by mouth daily	All patients except if not indicated as per nursing or medical team; e.g., those with congestive heart or renal failure with or at risk for fluid overload	1) Dehydration is delirium risk factor[64, 66] 2)Hi pulse&low BP assoc w/delirium[65] 3)Rehydration may be effective[19, 34]	86% (178 refusals; 80 off floor or unavailable; 25 medical contraindicat)
Undernutrition	1) Provision of snack 2) Meal assistance	All patients receive snack unless 15 min before or after a meal	Undernutrition associated with delirium[67]	70% (385 refusals; 81 off floor or unavailable)
Sleep/relaxation	Sleep and relaxation protocol: massage, warm drink, quiet music	Patients who report sleep difficulties to intervention team	Avoiding sedative effective[19]	80% (34 off floor /unavail; 12 time limit)
Medications	Medication alerts to medical team of meds associated w/delirium	All patients.	1) AGS criteria meds assoc w/ delirium[63] 2) Med review effective[35]	--

*Per visit adherence data during 2434 visits, with top reasons patient did not receive a component.

C.5 Outcomes and variables. For intervention and control patients, a trained RA will use the Confusion Assessment Method (CAM), a widely-used, validated measure,[57] to ascertain incident delirium each weekday during treatment of the acute illness and for 7 days afterward. Delirium severity will be ascertained using the Delirium Index (DI), which has been shown to be reliable in patients with and without underlying dementia and its validity tested in a nursing home population.[6, 58] Cognitive and physical function will be ascertained using the nursing home Minimum Data Set (MDS) Cognitive Performance[68] and Activities of Daily Living[69] scales, and the Brief Interview of Mental Status[70] at illness onset and 1 month after illness onset. These scales have been tested in the nursing home population and they are performed quarterly in all Medicare-certified facilities, making it possible to collect values on these measures from the medical record and establishing a pre-acute

illness baseline. The RA will collect data by medical record review on demographic and clinical characteristics, characteristics of the acute illness, delirium risk, and hospital use (Table 2). Spanish language versions of cognitive test items have been obtained from developers of the delirium and cognitive instruments whenever available. We have developed Spanish versions of other items by iterative translation and back-translation.

Table 2. Outcomes and variables

Data	Source	Instrument or Measurement	Frequency or time point
Outcomes			
Delirium and delirium severity	Research assessment	Confusion Assessment Method (CAM);[57] Delirium index (DI)[58]	Weekdays during illness & for 1w after illness end
Cognitive functional decline	Medical record, research assessment	Minimum Data Set Cognitive Performance scale;[68] Brief Interview of Mental Status[70]	Pre-illness assessment, illness onset, illness end, 1m after illness onset
Physical functional decline	Medical record, research assessment	Minimum Data Set Activities of Daily Living scale[69]	Pre-illness assessment, illness onset, illness end, 1m after illness onset
Hospital use	Medical record	Hospital admission	Between illness onset & 1m after illness onset
Descriptive			
Demographics	Medical record	Age, gender, race/ethnicity	Enrollment baseline
Chronic illness	Medical record	14 chronic conditions (count)	Enrollment baseline
Acute illness	Medical record	Diagnosis and severity (Severity Score[71])	Acute illness onset
Delirium risk	Medical record; research assessment	Delirium risk score (↓vision, cognitive impairment, severe illness,↑BUN/creat)[9]	Acute illness onset
Intervention components received	Elder Life Specialist visit form	Component implemented that was indicated; reasons not implemented	During acute illness (intervention group only)
Intervention "dose"	Elder Life Specialist visit form	Frequency (n) of Elder Life Specialist visits; duration (min) of visits	During acute illness (intervention group only)

C.6 Power and effect size. Based on our previous studies and the known impact of HELP on delirium,[19] we hypothesize observing a clinically meaningful 40-60% relative reduction in new delirium from 35% to between 15% and 20%. Power calculations have been performed treating delirium as a binary (CAM) and continuous (DI) outcome and accounting for clustering of observations by unit and for correlations over time. For the binary variable, new delirium is defined as when delirium occurs any time during the illness period. Sample size was calculated (Figure 1) with the continuity correction,[72-73] with assumed reliability (R)=.72; groups (g)=2; cluster size (by unit)=18; intracluster correlation (ICC)=.01; and variance inflation factor (VIF)=1+(cluster size-1)*ICC =1.17. With α=.05 and ρ (estimated average correlation of the outcome measures over time)=0.60, a sample size of 150 per group will provide 80% power to detect a group difference in new delirium from 35% (baseline)

Figure 1. $$n' = \frac{\left(z_{\alpha/2}\sqrt{2\bar{P}\bar{Q}} + z_{\beta}\sqrt{P_1Q_1 + P_2Q_2}\right)^2}{\left(P_2 - P_1\right)^2};\quad n = \frac{n'}{4}\left(1 + \sqrt{1 + \frac{4}{n'\left|P_2 - P_1\right|}}\right)^2,$$ where $\bar{p} = \frac{1}{2}(p_1 + p_2)$ and $\bar{q} = 1 - \bar{p}$

to 18% (intervention). If the usual care group also has a small reduction in delirium to 30%, with 150 per group it will be possible to detect a reduction to 13.5% in the intervention group, a 55% relative reduction. Thus, 150 subjects per intervention group will provide sufficient power to detect the hypothesized difference between groups. Power was also examined using the sample size formula for the log-rank test. Assuming a VIF of 117%, α=.05, and ρ=.60, given the same scenarios as above, with a sample size of 150 per group and power 80%, the detectable λ (hazard ratio) is 2.9. For the continuous measure (DI), power calculations are based on an assumed σ (population pooled standard deviation) of 3.12, using data from our previous study. The effect size estimate is: δ (DI group difference) and d= δ/σ (where d is Cohen's d). Adjusting for clustering and reliability, the detectable endpoint difference with a sample size of 150 is 1.29 with Cohen's d of 0.41, a moderate effect size. The sample size was also estimated for rate of change of the DI measure over five waves of data (Table 3). Based on data from our previous study, correlations among DI scores over waves (days) averaged 0.5 to 0.6. Thus, ρ is set at .50, .55 and .60. The DI point reduction per day in the intervention group vs. control was posited as δ= .24-.27. This translates to a

Table 3. DI correlation	n (δ=0.27)	δ (n=150)
ρ=0.6	117	0.238
ρ=0.55	132	0.252
ρ=0.5	146	0.266

Figure 2. $$S_x^2 = \sum (t_i - \bar{t})^2 / 5 = 10/5 = 2;\quad n^* = \frac{2\sigma^2(1-\rho)\left(z_{\alpha/2} + z_{\beta}\right)^2}{T_n s_x^2\ \delta^2}$$

total difference between control and intervention of 1.08 and d= δ/σ = .35 (where δ is reduction per day and d is Cohen's d for rate of change). Using the formulas in Figure 2,[74] with Tn=5 time points (baseline and 4 follow-up days), adjusting for reliability and clustering, and with 150 per group, under intent-to-treat (ITT), effect sizes from .238 to .266 are detectable, depending on correlation between waves, translating to a 1 point reduction in DI (medium effect size), with α=.05 and 1-β=.80.

C. 7. Analysis Aim 1: The primary analysis for the binary outcome will be logistic regression (SAS, PROC GLIMMIX) to test the hypothesis that those assigned to the intervention will have significantly lower rates of delirium compared to those assigned to usual care. The clustering design effect will be modeled. The need for inclusion of covariates resulting from examination of potential sources of bias will be determined. Predicted values from these analyses will be included as covariates in the logistic regression analyses, if necessary. The continuous DI variable will be examined using slope analyses and the repeated measures ANCOVA model in SAS PROC MIXED. This method will allow for more flexible modeling of assumptions, treatment of missing observations and inclusion of all subjects with at least one wave of data, and the inclusion in the analysis of participants who do not complete follow-up assessments (on an ITT basis). Aim 2: The primary analysis for the binary outcome will be logistic regression to test the hypothesis that characteristics of the intervention (e.g., longer visits, components delivered) will be associated with less delirium, using only the intervention group sample and adjusting for covariates as needed to correct for imbalances, since in this case exposure is not assigned. Similar to Aim 1, the clustering design effect will be modeled. The continuous DI variable will be examined using slope analyses and the repeated measures ANCOVA model in SAS PROC MIXED. Bias and missing data: We do not expect significant drop-out in this study since it was not observed in our prior study with the 1-month follow-up period. Attrition bias: We will use baseline assessment information to compare completers and dropouts with regard to sociodemographics and other covariates. A logit model of attrition will be developed and the predicted values from this model used as a covariate to adjust for differential attrition. Treatment of missing data: Using the maximum-likelihood approach we will include baseline data, and we will try to obtain follow-up data from all randomized patients so non-completion will not result in loss to follow-up.

C.8 Data collection, blinding, and study monitoring. The RA will enroll patients and provide enrollment information to the DCC and PI. The PI will notify the intervention team of enrolled intervention patients. Follow-up data collection (Appendix 3) will come from facility electronic medical record and MDS, patient observation, patient interview -- for which there are English and Spanish script versions -- and staff interview. The RA will be English/Spanish bilingual and will be trained 1) on the content and coding of each data element, data handling procedures, and protocols to handle possible problems and 2) in interview skills and referral procedures for participants who indicate symptoms that might require immediate medical assistance. The RA will enter data into protected computer files with software that contains edits for out-of-range entries, to prompt correction. Data are in password-protected, encrypted environments and are made available to the analytic programmers through a secure file-sharing website. *To maintain RA blinding we will 1) assign the RA to supervision by a different department (the research department) from intervention staff (nursing department), 2) keep the RA and intervention staff unaware of each others' presence and roles, 3) keep the RA and intervention staff unaware of study aims and hypotheses, and 4) schedule separate intervention and RA shifts on the units to avoid overlap on a unit at the same time. At study end we will test for blinding success by asking the RA to guess intervention and control assignments.* The PI will provide oversight of study activities and blinding activities following Jewish Home Lifecare IRB committee requirements to ensure study safety. A 3-person advisory group meeting every 4-6 months will provide guidance on data and safety issues, decisions and challenges to study implementation, intervention refinement, and disseminating results.

C. 9 Strengths and limitations Study strengths are its innovative intervention, the clinical importance of delirium in this setting, the expertise of the investigators, and pilot work that supports study feasibility. Study limitations include the single site, limiting general applicability, and the limited sample size, limiting power to address all important outcomes. However, if this study is positive, it lays the groundwork for a future study that is multi-site that can produce information on additional outcomes and cost. The study is also important if no effect is observed, or if it yields findings on components that suggest a need to modify the intervention.

Workplan and timeline (All steps to be overseen by Boockvar, w/input by Inouye, Teresi, and advisory group)

Project Year	Pre-	1			2	
Year	fund	2015	2016			2017
Study Activities Month Starting	Apr	Jun	Jan		Jul	Jan
Hire and train RA and intervention CNAs (Boockvar, Data Coord. Cent.) (3 mo)	XXX					
Establish protocols, randomly assign units (Boockvar, Inouye, DCC) (3 mo)		XXX				
Enroll patients, provide intervention, collect /enter data (RA,CNAs, DCC) (19 mo)		XXXXX	XXXXXX		XXXXXX	XX
Analyze data, including interim safety analysis (adv grp, Teresi, DCC) (4 mo)				X		XXX
Reports, dissemination, next grant preparation (Boockvar, Inouye, Teresi) (3 mo)						XXX