

TRAIN-AD (Trial to Reduce Antimicrobial Use In Nursing home residents with Alzheimer's disease and other Dementias)

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## **2 PRÉCIS**

### **2.1 Study Title: TRAIN-AD (Trial to Reduce Antimicrobial Use In Nursing home residents with Alzheimer's disease and other Dementias)**

### **2.2 Objective**

Conduct a cluster randomized controlled trial of an education and training intervention on infection management outcomes of 480 residents with advanced dementia (N=240/arm) in 24 Boston-area nursing homes (NHs) (N=12/arm).

### **2.3 Design and Outcomes**

### **2.4 Design**

36 month cluster randomized controlled trial (RCT) to evaluate a multicomponent intervention that merges best practices in infectious diseases and palliative care to improve infection management for suspected urinary tract infections (UTIs) and lower respiratory tract infections (LRIs) among 480 advanced dementia residents (240/arm) living in 24 Boston area nursing homes (NHs) (12/arm). Randomization and intervention implementation will be at the facility level. Outcomes will be measured at the resident level.

### **2.5 Outcomes**

The following 12-month outcomes related to suspected UTIs and LRIs will be compared between the intervention and control arms (usual care):

#### **PRIMARY OUTCOME:**

- I. Total number of antimicrobial courses for suspected UTIs and LRIs/person-year

#### **SECONDARY OUTCOMES:**

- II. Number of antimicrobial courses prescribed for suspected UTIs and LRIs when minimal criteria for treatment initiation were absent based on consensus guidelines/person-year
- III. Advance care planning about infection management over 12 months defined as a documented discussions between proxies and providers or a new advance directives to withhold antimicrobials by any route oral, intramuscular, or intravenous.
- IV. Number of burdensome procedures used to evaluate suspected LRIs and UTIs (hospital transfer, bladder catheterization, chest x-ray, and blood draws)/person-year.

### **2.6 Interventions and Duration**

Each facility will participate for a total of 27 months, including a 3-month start-up/planning period and 24 month intervention implementation (intervention NHs only) and data collection period. Residents will be enrolled during the first 12-months at each facility, and each resident will be followed for up to 12 months.

The intervention has two main components, provider training and proxy education.

1. Provider Training: Multifaceted approach to education of providers with direct care responsibilities for patients with advanced dementia. Components include:
  - a. In-person training
  - b. On-line course
  - c. Infection management algorithms
  - d. Guidelines for communicating with proxies
  - e. Prescribing feedback
2. Proxy Education: A booklet mailed to proxies of residents with advanced dementia describing issues related to infection management in advanced dementia upon resident enrollment in study.

## **2.7 Sample Size and Population**

The study sample will included 480 NH resident with advanced dementia (N=240/arm). *See statistical analytic protocol (SAP) for a full explanation of sample size calculations.*

### **3 STUDY TEAM ROSTER**

#### **3.1 Principal Investigator**

##### **Susan Mitchell, MD, MPH**

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Professor of Medicine, Harvard Medical School  
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Role: Lead investigator on all aspects of the trial. Working with other members of the research team and with outside resources, Dr Mitchell has developed and designed the implementation of all aspects of the TRAIN-AD program. Dr. Mitchell will direct the overall logistics of the study, including: recruitment of nursing homes, field operations, and data collection, management, and analyses. As HSL is the prime institution for the grant, Dr. Mitchell will be the project's primary liaison to the NIH and oversee regulatory activities (primary Institutional Review Board approval, coordination of Data Safety and Monitoring Board (DSMB)). Her involvement as both a clinician and investigator is essential to the success of this project.

#### **3.2 Co-Investigators:**

##### **Erika D'Agata MD, MPH**

Infection disease specialist and epidemiologist, Rhode Island Hospital  
Associate Professor of Medicine, Brown University  
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Phone: 401-444-5113, Fax: 401-444-4061  
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Role: Co-investigator, works with Dr. Mitchell to develop and implement the TRAIN-AD program. D'Agata will take primary responsibility for the intervention implementation in the nursing homes and assist Dr. Mitchell with the overall management and conduct of this project, training and supervising of staff in data collection, guiding the analysis, presenting the work at national meetings and preparing the work for publication.

**Laura Hanson, MD, MPH**

Professor, Geriatric Medicine, University of North Carolina, Chapel Hill

Address: 5003 Old Clinic Road, Chapel Hill, NC, 27599

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Email: [lhanson@med.unc.edu](mailto:lhanson@med.unc.edu)

Role: Co-investigator, working helping to optimize program planning and implementation, providing on-going expertise on study design, intervention design, and data analysis.

**Michele Shaffer, PhD**

Associate Professor, Seattle Children's Hospital, Biomedical Statistics

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Phone: 206-884-1423

Email: [michele.shaffer@seattlechildrens.org](mailto:michele.shaffer@seattlechildrens.org)

Role: Study statistician who remains blinded throughout the trial. Dr. Shaffer has helped in the analytic design, randomization scheme, and power calculations for this application, and will continue to provide statistical leadership as the study progresses. She will supervise the data analyses, prepare and maintain the trial statistical analytic plan, and assist in the preparation of data for presentations, data safety monitoring board reports, and publications..

**3.3 Consultants**

**Ruth Anderson, PhD**

Associate Dean for Research, University of North Carolina, School of Nursing

Address: Carrington Hall, Chapel Hill, NC, 27599

Phone: 919-966-8785

Email: [rutha@email.unc.edu](mailto:rutha@email.unc.edu)

Role: Consultant working with investigators to optimize intervention roll-out. Dr. Anderson is an expert in the application of complexity science and the adaptive leadership framework to research aimed at improving the quality of care for older adults in long term care. She helped develop the implementation plan for this trial and will continue to provide guidance on how the research field staff can best work with the nursing home leadership to adapt the intervention implementation in their nursing homes.



### **3.4 Research Team Members:**

#### **Elaine Bergman, MGS**

Project Director, Institute for Aging Research, Hebrew Senior Life

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Phone: 617-971-5335

Email: [elainebergman@hsl.harvard.edu](mailto:elainebergman@hsl.harvard.edu)

Role: Project manager; main responsibilities for the proposed project will include, i. lead all organizational processes (e.g., create time and events chart, coordinate all meetings), ii. Create and maintain all essential trial documents (e.g., protocol, manual of operating procedures), iii. Manage human subjects and data safety documentation, iv. Supervise the creation of REDCap data collection instruments, v. coordinate provider on- line course registration and completion with Harvard Medical School Department Continuing Medical Education, and vi. Supervise tracking of all protocol elements (recruitment, data collection).

#### **Ruth P. Carroll, RN**

Project Director, Institute for Aging Research, Hebrew Senior Life

Address: 1200 Centre Street, Boston, MA 02131

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Role: Project field director for the project and co-lead the implementation of the intervention in the experimental facilities. Ms. Carroll will recruit all nursing homes, serve as a liaison between the NH administrators/facility site champions and the research team, coordinate subject enrollment, and supervise the intervention implementation.

#### **Daniel Habtemariam, MPH**

Data Analyst, Institute for Aging Research, Hebrew Senior Life

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Role: Help develop and manage REDCap electronic data capture systems, prepare weekly data collection tracking schedules for the field staff, generate monthly recruitment tracking reports, prepare data for DSMB reports, create the analytic file, and assist Dr. Shaffer perform the data analyses.

**Tim Tsai**

Programmer/Data Analyst, Institute for Aging Research, Hebrew Senior Life

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Role: Data analyst; member of data team which develops and produces data analytics including recruitment and ongoing data collection, NIH and data safety reports throughout the trial; maintains project report site and ongoing event tracking.

**Maliaka Lindsey, LPN**

Research Assistant

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Role: Responsible for screening subjects, conducting baseline nurse interviews to ascertain the residents' functional status (~ 1 minute/interview), and conduct all chart reviews (~20 minutes/review).. Maintenance of participant code sheet/database within each participating facility.

**Andrea Loizeau**

Doctoral student

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Role: Assists with intervention planning and implementation.

**Erin Scott, MD**

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Role: Physician educator, will lead training seminars in intervention NHs

**Erin Stevens, MD**

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Role: Physician educator, will lead training seminars in intervention NHs

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Role: Physician educator, will lead training seminars in intervention NHs

## **4 PARTICIPATING STUDY SITES**

The study is being conducted at 24 NH Boston area NHs. Eligible homes must have at least 60 long stay beds and be within 60 miles of Boston. Sites are recruited from a pool of 95 eligible NHs in the Boston area. Recruitment, randomization and study enrollment will be done in 4 waves over a 12-month period, with each wave starting three months apart. In each wave, 6 NHs will begin the study (3 Control NHs and 3 Intervention NHs/wave).

## **STUDY OBJECTIVES**

### **4.1 Primary Objective**

Aim 1. To conduct a cluster RCT of an intervention to improve infection management among 480 residents with advanced dementia (N=240/arm) residing in 24 NHs (N=12/arm) and compare the total number of antimicrobial courses for suspected UTIs and LRIs/person-year (primary outcome) over 12 months in the intervention vs. control (usual care) arms. Data will be obtained from review of the residents' charts and medication administration records q2months up to 12 months.

*H1. The number of antimicrobial courses/person-years will be lower in the intervention vs. control arms.*

### **4.2 Secondary Objectives**

Aim 2. To compare the number of antimicrobial courses prescribed for suspected UTIs and LRIs when minimal criteria for treatment initiation are absent based on consensus guidelines/person-year in the intervention vs. control arm over 12 months.

*H2. The number of courses prescribed when minimal criteria are absent /person-year will be lower in the intervention vs. control arm.*

Aim 3. To compare the following 2 outcomes in the intervention vs. controls arms over 12 months: i. Advance care planning about infection management (e.g., documented discussions between proxies and providers, advance directives to withhold antimicrobials), and ii. Number of burdensome procedures used to evaluate suspected LRIs and UTIs (hospital transfer, bladder catheterization, chest x-ray, blood draws)/person-year.

*H3a. Advance care planning about infections will be higher in the intervention vs. control arms.*

*H3b. The number of burdensome procedures/person-days will be lower in the intervention vs. control arms.*

## **5 BACKGROUND AND RATIONALE**

### **5.1 Background on Condition, Disease, or Other Primary Study Focus**

The advanced stage of Alzheimer's disease and other dementias is characterized by the onset infections, which prior work suggests are widely mismanaged. Antimicrobials are extensively prescribed, most often without evidence to support a bacterial infection. Antimicrobial exposure is the main factor leading to multidrug-resistant organisms (MDROs); a growing public health threat. Moreover, the benefits of antimicrobials remain unclear for patients with advanced dementia, for whom infections are often a terminal event and comfort is most commonly the goal of care.

In 2015, our group completed the **Study of Pathogen Resistance and Exposure to Antimicrobials in Dementia (SPREAD)** which prospectively examined antimicrobial use and MDRO acquisition in 363 NH residents with advanced dementia.<sup>9,22</sup> Antimicrobials were prescribed for 72% of suspected infections, but only 44% of these episodes met guideline-based criteria for treatment.<sup>23</sup> Suspected urinary tract (UTIs) and lower respiratory tract (LRIs) accounted for 94% of mistreated episodes. Criteria were more likely to be met when the residents' proxies were counseled about antimicrobials. Two-thirds of residents were colonized with MDROs. Antimicrobial use was the major risk factor for MDRO acquisition. Motivated by these findings, we conducted a pilot study (NIH R21) of a multi-faceted intervention to improve management of suspected UTIs and LRIs. Unlike standard NH antimicrobial stewardship programs,<sup>18,24</sup> The intervention merged best practices in infectious diseases and palliative care, and targeted this unique population for whom the need and opportunity to improve infection management are particularly compelling.

### 5.1.1 Epidemiology

In the Choices, Attitudes, Strategies and Care of Advanced Dementia (CASCADE) study, led by Dr. Mitchell, 41% of participating NH residents with advanced dementia had suspected pneumonias and 53% had febrile episodes over 18 months.<sup>1</sup> In SPREAD, we found 66% of NH residents with advanced dementia had suspected infections over 1 year, most often UTIs and LRIs.<sup>9</sup> Approximately 50% of advanced dementia patients are diagnosed with pneumonia in the last 2 weeks of life.<sup>8,9</sup> The 6-month mortality rate following pneumonia is 50%.<sup>1,34</sup>

Antimicrobial use is extensive.<sup>6,8,35-37</sup> In prospective studies, 52-66% of NH residents with advanced dementia received antimicrobials over 12 months, and 42% in the last 2 weeks of life.<sup>9,37</sup> Much of this use may be inappropriate as antimicrobials are often started without adequate clinical evidence to support a bacterial infection.<sup>9-15,23,38</sup> Infections are often treated empirically in NHs without the benefit of objective tests (e.g., cultures). Thus, the Society for Healthcare Epidemiology of America endorsed minimal clinical criteria to initiate antimicrobials in NHs.<sup>13</sup>

### 5.1.2 Advanced dementia patients are reservoirs for multidrug resistant organisms (MDROs)

The emergence of MDROs is a major public health threat,<sup>39-44</sup> and growing concern in NHs.<sup>14,16,19,45-47</sup> Between 43-62% of NH residents are colonized with either methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, or multidrug-resistant gram-negative bacteria.<sup>48,49</sup> MDRO colonization in NHs is associated with increased mortality,<sup>50-53</sup> costs,<sup>54</sup> hospitalizations.<sup>55,56</sup> NH residents bring MDROs into hospitals.<sup>57-59</sup> Our prior work showed that advanced dementia residents are 3 times more likely to have MDROs than other residents.<sup>17</sup> In SPREAD, we found 64% of the cohort was colonized with MDROs over 12 months.<sup>9</sup> Antimicrobial exposure is the strongest risk factor for MDRO acquisition,<sup>49,51,53,60-64</sup> Thus, reducing antimicrobial misuse in advanced dementia is a key opportunity to limit MDROs colonization in the NH setting.

### 5.1.3 Benefits and burdens of treatment

Two potential benefits may motivate treating suspected infections in advanced dementia; prolonging life and symptom relief. In the absence of RCTs, observational studies help inform decision-making regarding these outcomes.<sup>6,21,65-68</sup> In CASCADE, residents with pneumonia

treated with antimicrobials lived longer, but had more discomfort, than those who were not treated.<sup>6</sup> In SPREAD, treating suspected UTIs with antimicrobials had no effect on survival.<sup>21</sup> Both the work-up and treatment of infections can be burdensome for these frail patients.<sup>69</sup> In SPREAD, 74% of suspected infections involved a bladder catheterization, hospital transfer, blood draw, or chest x-ray.<sup>69</sup> Infections are the most common reason advanced dementia patients are hospitalized<sup>70</sup> but can often be managed with similar efficacy in the NH.<sup>6, 71, 72</sup> Even oral antimicrobials may cause discomfort, as these patients often have swallowing problems. Finally, older patients are more susceptible to adverse effects of antimicrobials such as *Clostridium difficile* infections, allergic reactions, MDRO acquisition, and drug-drug interactions.<sup>6, 37, 65, 73-75</sup>

#### 5.1.4 Treatment must align with the goals of care:

A-quarter of all treatment decisions faced by proxies of NH residents with advanced dementia relate to infections.<sup>76</sup> Given the burdens and questionable benefits of antimicrobials, infection management should be approached using a framework of shared decision-making similar to other end-of-life treatment choices.<sup>77-80</sup> This approach requires adherence not only to infectious disease guidelines, but also to the goals of care (e.g., life prolongation or comfort). In prior work, over 90% of proxies state comfort is the goal of care.<sup>1, 9</sup> For these patients, the burdens of assessing and treating infections may outweigh the benefits, particularly when the likelihood of a bacterial infection is low.

Several features characterize optimal shared decision-making. Ideally, counseling should be done as part of advance care planning rather than at the time of a crisis, and preferences documented in advance directives, such as the Physician Orders for Life Sustaining Treatment (POLST) form.<sup>81</sup> Proxies should be told to expect infections in end-stage disease, apprised of what an appropriate evaluation entails, and cautioned about common pitfalls leading to unnecessary antimicrobial use (e.g., asymptomatic bacteriuria). The benefits and burdens of evaluating and treating suspected infections should be presented, and the option of a purely palliative approach described (e.g., analgesics, antipyretics). Finally, providers should help proxies align the management approach with the goal of care. If the goal is to optimize comfort, it is reasonable to suggest that no evaluation be initiated for infections and palliation provided. For the minority of patients for whom the goal remains to prolong life, evaluation and treatment is reasonable but only when there is adequate clinical evidence to support a bacterial infection. Optimal decision-making does not routinely occur in practice, but when it does, data suggest care is improved. In SPREAD, only 45% of proxies were asked about preferences for antimicrobial use, and only 34% were counseled to expect infections or about treatment options. However, when they were counseled, minimal criteria for initiating antimicrobials were more likely to be met.<sup>9</sup>

#### 5.1.5 Interventions to improve infection management in advanced dementia:

The need to improve infection management in the general NH setting is well-recognized,<sup>10, 24</sup> as reflected in The Centers for Disease Control's (CDC) recent call to expand antimicrobial stewardship activities in NHs.<sup>18</sup> Although many NH residents have advanced illnesses, this CDC initiative as well as most standard NH antimicrobial stewardship programs, focus solely on infectious disease guidelines,<sup>46, 72, 82-87</sup> and fail to integrate patient preferences or palliative care principles into prescribing algorithms, training materials, and evaluation metrics. At the same time, a growing literature has highlighted concerns about infection management at the end-of-life.<sup>88</sup> Our intervention merges best practices in infectious diseases and palliative care, and

focuses on a unique subset of NH patients for whom the need to improve infection management is particularly compelling.

While not focused on advanced dementia, prior antimicrobial stewardship NH research informs our study design.<sup>46, 72, 82-87</sup> Loeb conducted two cluster RCTs in 22 Ontario NHs. In one, a facility-wide intervention to improve UTI management reduced antimicrobial use.<sup>82</sup> In the other, a clinical pathway for LRIs resulted in fewer hospitalizations.<sup>72</sup> These studies and others,<sup>46, 72, 82, 86, 87, 89</sup> demonstrate that rigorous RCTs of NH interventions to improve infection management can be conducted and improve outcomes. Most successful interventions have multiple components, and include prescribing feedback to providers to motivate behavior change.<sup>18, 24, 86, 87, 89, 90</sup> More recent efforts have also recognized that for interventions to be adoptable and sustainable, they must target the many interacting factors that influence NH care, and engage key stakeholders (e.g., medical providers, nurses, families, administrators) in learning, communication, self-monitoring, and on-going adaptation.<sup>86, 87, 91, 92</sup> One pilot study of a quality improvement program incorporating these features in 12 NHs significantly reduced antimicrobial prescriptions.<sup>86, 87</sup>

#### 5.1.6 Summary of significance.

The significance is summarized as follows: 1. Advanced dementia is a leading cause of death. Most patients receive their care in NHs; 2. Advanced dementia residents are commonly suspected of having infections, for which antimicrobials are extensively prescribed. Minimal criteria to support a bacterial infection are absent for most treated episodes; 3. These residents are reservoirs for MRDOs. Antimicrobial use is the main risk factor for MDRO colonization; 4. As these residents are in the terminal phase of dementia, they may not clinically benefit from antimicrobials, especially when the likelihood of a bacterial infection is low; 5. Comfort is the goal of care for > 90% of these residents. The burdens associated with work-up and treatment of infections, generally do not promote comfort; 6. Most proxies are not counseled about infection management, but when they are, antimicrobials are more likely to be used in accordance with guidelines; 7. NH interventions to improve infection management can be successfully tested in RCTs, but to be sustainable they must target the many factors that influence NH care, 8. Traditional NH antimicrobial stewardship programs do not include patient preferences or palliative care principles; and 9. TRAIN-AD builds on prior work and address the existing gaps, by applying state-of-the-art methodology for cluster RCTs<sup>95, 96</sup> and conceptual underpinnings for successful program implementation in NHs,<sup>86, 87, 91, 92, 97</sup> to evaluate an intervention that merges best practices in infectious diseases and palliative care in a unique population for whom the need and opportunity to improve infection management is especially compelling.

With this foundation and leveraging a network of NHs and research infrastructure established in 4 prior NIH R01s, TRAIN-AD (Trial to Reduce Antimicrobial Use In Nursing home residents with Alzheimer's disease and other Dementias), is a cluster randomized controlled trial (RCT) of an intervention to improve infection management in advanced dementia. All intervention components integrate infectious disease and palliative care principles.

## **6 STUDY DESIGN**

This cluster RCT will evaluate an infection management education and training program targeting direct care providers and proxies of residents with advanced dementia, on infection management in 480 (Control=240/ Intervention=240) patients 60 years or older with advanced

dementia residing in 24 (12 Control/12 Intervention) participating Boston area nursing homes. The unit of randomization is the facility but the unit of analysis is the patient, clustered within the facility. The intervention will be implemented facility-wide, thus all patients with advanced dementia, cared for in the NHs during the 24-month implementation period are potential subjects in this study. Data will be obtained from bi-monthly chart review of enrolled eligible residents for up to 12 months.

Outcomes to be compared between patients in the intervention and control NHs include: total number of antimicrobial courses for suspected UTIs and LRIs/person-year (primary outcome) over 12 months in the intervention vs. control (usual care) arms (Aim 1), number of antimicrobial courses prescribed for suspected UTIs and LRIs when minimal criteria for treatment initiation are absent based on consensus guidelines/person-year (secondary outcome) in the intervention vs. control arm over 12 months.(Aim 2), and : i. advance care planning about infection management (e.g., documented discussions between proxies and providers, advance directives to withhold antimicrobials), and ii. Number of burdensome procedures used to evaluate suspected LRIs and UTIs (hospital transfer, bladder catheterization, chest x-ray, blood draws)/person-year (Aim 3)

## **7 SELECTION AND ENROLLMENT OF PARTICIPANTS**

The intervention will be rolled out facility-wide. Participation occurs at 3 levels. Nursing homes will be recruited, randomized and enrolled into the study. Site administrators who agree to participate in the study will serve as gatekeepers within their facility. Providers will be recruited to participate in the infection management training program, and eligible residents will be enrolled for ongoing chart reviews to assess program effect on infection management.

### **7.1 Inclusion Criteria**

#### **7.1.1 Facility inclusion criteria**

- 1) More than 60 beds
- 2) Within 60 miles of Boston

#### **7.1.2 Resident inclusion eligibility criteria**

- Age > or = to 60 years
- A diagnosis of dementia (any type)
- Global Deterioration Scale (GDS) score of 7
- NH length of stay >90 days
- An individual who can communicate in English has been formally or informally designated as a health care proxy
- Not comatose

GDS stage 7 features include: profound memory deficits (cannot recognize family), total functional dependence, speech  $\leq$  5 words, incontinence, and non-ambulatory. GDS 7 was chosen to define advanced dementia as it has been successfully operationalized and validated in or prior studies, and experts agreed to use this definition in research studies. A 90 day minimum length of stay was chosen to exclude short-stay patients.

### 7.1.3 Provider inclusion criteria

TRAIN-AD intervention will target the “usual” providers including nurses, MDs, NPs and PAs routinely caring for advanced dementia patients. Nurses should be providing care for these residents for a minimum of 2 shifts most weeks. MDs, NPs, and PAs should have at minimum 2 residents with advanced dementia on their regular resident panel. We estimate there will be 15-20 targeted providers/NH (12-16 nurses, 1-3 physicians, 0-3 NPs/PAs).

Eligibility criteria for providers in the intervention nursing homes include:

- Direct care provider of advanced dementia residents (a nurse, nurse practitioner, physician or physician assistant identified by a senior administrator as an individual who cares for residents with advanced dementia)
- Can communicate in English (because intervention materials are all in English),
- Over 21 years of age.

## 7.2 **Exclusion Criteria**

### 7.2.1 Facility exclusion criteria

- Population not primarily English speaking
- Evidence of institutional instability at time of recruitment

### 7.2.2 Provider exclusion criteria

- Do not provide direct care to residents with advanced dementia
- Not a “usual” provider within the NH (i.e. visiting hospice provider)
- Does not speak English
- Is less than 21 years old

### 7.2.3 Resident exclusion criteria

- Less than 60 years of age
- Living in nursing home for less than 90 days
- Does not meet GDS score of 7
- Does not have a proxy that communicates in English
- Proxy has communicated wish to opt-out of study
- Resident has fallen into a coma or has expired prior to baseline

## 7.3 **Study Enrollment Procedures**

### 7.3.1 Facility Enrollment

A total of 24 Boston area NHs will be recruited from a pool of 95 eligible NHs in the Boston area. NHs will be recruited, randomized and enrolled into the study in groups of 6 (3 Control / 3 Intervention) every 3 months for one year. The project director will mail study information and a recruitment letter to the senior administrators of eligible NHs. The letter introduces the intervention and implications of participation including randomization. One week after the



mailing, the project director contacts the NHs' administrators by telephone to answer questions and seek their participation. Face to face meetings to further explain the study are held with administrators upon request.

One month before the three-month planning period is scheduled to start, the list of 6 newly recruited homes will be randomized. (*see SAP for details on randomization procedures*). Immediately following randomization, the project director contacts each facility informing them of their study assignment and initiating the 3-month planning procedures.

#### 7.3.1.1 Facility Randomization and Stratification Procedures: *See SAP*

#### 7.3.2 Provider Recruitment

The research team works with the intervention NH leadership team and designated site champion to facilitate provider recruitment and orientation throughout the intervention period. At the start of the intervention and every 6 months throughout intervention period, the project director requests a list of eligible providers from the site champion. The research team sends a packet of information to the providers introducing the trial, and providing them with intervention materials, contact information, and information related to upcoming TRAIN-AD training seminars. All aspects of provider participation are optional. They can chose to participate in all, some or no aspects of the intervention, and can request exclusion at any time by contacting the research project manager, whose contact information is provided in all outreach materials.

#### 7.3.3 Resident Enrollment

We have obtained an IRB waiver of individual authorization for disclosure of personal health information (PHI) to screen and identify eligible residents. At the start of the study and every 2 months for 12 months in each NH, the RA will interview unit nurses to identify eligible residents. Eligibility and proxy information will be confirmed by chart review. Within one week of eligibility screening, proxies of eligible residents in the intervention NHs will be mailed study information, including the infection management booklet and the project director's (PD's) contact information if they wish to opt out. In addition, flyers will be posted in ALL participating facilities (control and intervention) explaining that the study is being conducted and that it includes data collection from the charts of residents with advanced dementia. The flyers will include contact information for the PD to ask further questions and an opportunity for proxies to "opt-out". If proxies do not contact the PD within two weeks, the resident will be enrolled and included in bi-monthly chart review with data abstraction.

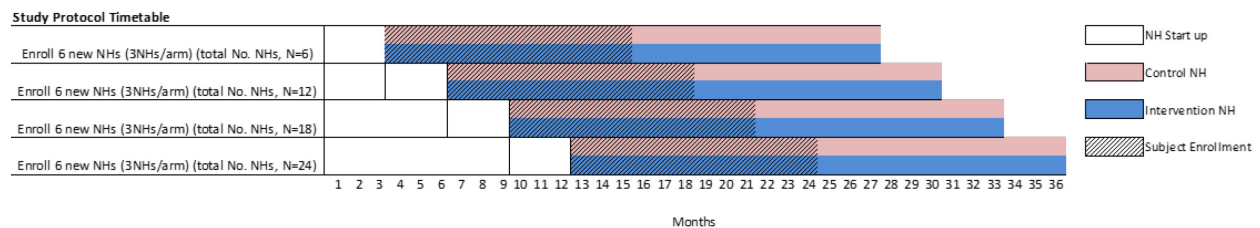
PHI will not be removed from the facility. For purposes of recording and tracking eligible residents, study IDs will be assigned to eligible residents at the point of eligibility screening. A code sheet containing the names associated with assigned study IDs will be stored in a secure location within the participating NH.

## **8 STUDY INTERVENTIONS ADMINISTRATION AND DURATION**

The entire trial will be conducted over 36 months, each intervention facility will be involved for 27 months which includes 3 months planning period 24 months of intervention implementation in each intervention NH (See below). At each facility residents will be enrolled for the first 12 months of the implementation period, and each resident will be followed for up to 12 months

Control homes will follow the same timeline for resident enrollment and data collection, while they continue to receive usual care. During the 3 month planning period, the research team works with the leadership and site champion in each NH to optimize program roll-out within each unique environment.

The study intervention is a multi-component training and education program targeting direct care providers and healthcare proxies for advanced dementia NH residents, intended to improve the management of urinary and lower respiratory tract infections in advanced dementia patients. In partnership with NH leadership, the intervention is rolled out as a new program within the facility. There are two components to this practice intervention: 1. Provider Training, and 2. Proxy Education. Intervention components aimed at the provider include: Professionally led infection management training seminars, online infection management course, and infection management guidance algorithms. Additionally participating prescribing providers will be sent bimonthly infection management feedback reports. Proxy Education is completed by providing an infection management in Advanced Dementia booklet to proxies of patients with AD upon resident enrollment in study.



## 8.1 Provider-directed Interventions

**Provider Training:** Multifaceted approach to education of providers with direct care responsibilities for patients with advanced dementia. Training initiatives focus on appropriate diagnosis and treatment of suspected UTIs and LRIs in patients with advanced dementia. All training initiatives include application of recommended diagnostic criteria, inclusion of goals of care in development of treatment plan, and provider communication training to optimize communication with healthcare proxies throughout the process. Communication training provided in the seminar and online course is further reinforced with provision of a communication tips pocket card.

### 8.1.1 In-person training:

At each NH during the start-up period and q6 months during the 24 month implementation period, the research team including a PI or trained physician educator, and one or both PDs will lead on-site 1-hour group training seminars to present principles of infection management in advanced dementia, intervention components, and approaches to proxy counseling. Seminars will include a didactic presentation, open discussion, and communication training for common challenging scenarios (e.g., proxy requesting a resident get antimicrobials when treatment is not clinically indicated). To enhance sustainability, TRAIN-AD site champions will be trained to conduct the seminar enabling him/her to co-lead on-going sessions and be an on-site resource to reinforce the intervention principles. Providers that are unable to attend the on-site training will be offered a condensed 1:1 training session at their convenience.

#### 8.1.1.1 Targeted attendees

All providers with primary care responsibilities for residents with advanced dementia (e.g., medical providers (physicians, NPs, PAs, nurses) and other key individuals (e.g., Director of Nursing (DON), infection control monitor) will be targeted to attend the seminars. See section 7.1.3 for description of provider eligibility criteria.

#### 8.1.1.2 Materials

Invited providers will be sent a training seminar packet prior to the seminar which includes items presented in the seminar and will serve as an ongoing resource for participants, and for those unable to attend, the in-person training.

#### 8.1.2 On-line course

The "Infection Management in Advanced Dementia" on-line course is being offered through the Harvard Medical School Department of Continuing Education (HMS DCE) and has been approved for CME credit. The PIs created this peer-reviewed course through an iterative process with experts in infectious diseases, palliative care, and geriatrics. The self-directed course consists of 4 virtual patient cases, 2 for UTIs and 2 for LRIs, with 3-4 multiple choice questions/case, and 3 communication training videos embedded within the course. Participants receive response-specific, evidence-based feedback, and complete a 12-item multiple-choice pre/post knowledge test. Providers including RNs, LPNs, NPs, PAs and MDs with direct care responsibilities for advanced dementia residents will be targeted to complete the course. Instructions on how to access the course will be in the orientation package and reviewed at the initial training. Participating providers will receive \$50 from the research team 1 CME credit for completing the course for which the usual \$50 will be waived.

Providers are encouraged to complete the course by the end of the first month following invitation. The course website provides the research team with provider participation data, to inform ongoing engagement efforts directed toward providers. Several strategies will be used to promote timely completion. Weekly reminders will be sent by the PD to non-participants for up to 1 month (mail/email) and the site champion will also be given the names of providers that have not completed the course to encourage their participation.

#### 8.1.3 Algorithms

Algorithms guiding appropriate antimicrobial initiation for suspected UTIs and LRIs that integrate palliative care principles and patient preferences are used throughout the training program and displayed throughout intervention NHs to reinforce provider learning. Laminated 5" X 7" pocket reference cards with the algorithms, will be given to providers in their orientation material packet and made available throughout the study.

#### 8.1.4 Prescribing Feedback Reports

A key component of the intervention is the provision of infection management feedback to prescribing providers within intervention NHs. This, prescribing feedback reports will be sent to all prescribing providers and the site champions based on data abstracted from the charts, including: 1. Proportion of residents given antimicrobials for suspected LRIs and UTIs when minimal criteria were absent in prior 2 months, and which criteria were absent, 2. Benchmarking

of inappropriately treated episodes for individual prescriber with other prescribers in the facility and in other intervention NHs, and 3. Time trends for these parameters.

## **8.2 Proxy Education:**

The goal for proxy education is to promote informed decision-making for resident care that is concordant with preferences, which is also desired goal for high quality nursing home care. At the time of resident enrollment, English-speaking proxies of enrolled residents will be sent a booklet written by the co-PIs, professionally reviewed and translated into 6<sup>th</sup> grade reading level that explains in a lay fashion: i. the nature of urinary and respiratory tract infections in advanced dementia, ii. Treatment options (antimicrobials vs. only comfort care), iii. Concerns about antimicrobial overuse, and iv. Features of appropriate antimicrobial use. Proxies will be sent the booklet following resident screening and encouraged to discuss infections in advanced dementia with their family member's direct care providers.

## **8.3 Handling of Study Interventions**

**Intervention Implementation:** The implementation plan aims to strike a balance between maximizing intervention adherence, and sustainability. While its components emphasize a standardized approach to UTIs and LRI management, NHs will have the opportunity to adapt implementation to their own environment. To increase likely program success, the research team will encourage ongoing communication between providers and proxies regarding infection management planning, and encourage integration of aspects of the infection management program into NHs' quality improvement programming. Various supports will be put in place to help sustain the program and support the NH implementation team. These supports include provision of information support for the site champions. A compendium of reference and guidance materials is provided to each site. Additionally, the research team will be available to site champions for ongoing support through monthly huddles and one on one check in calls. Finally, members of the research implementation team will meet with the NH implementation and leadership team every 3 to 6 months to review program implementation and optimize as necessary.

## **8.4 Facility Start-Up**

Program start up within all participating nursing homes will happen over three month periods.

### **8.4.1 Control home Start-up**

Following randomization, the project director contacts the administrator to inform them of the facility's research assignment, facilitate a brief environmental scan questionnaire, and schedule a brief (30 minute) in-service for the leadership team and staff to introduce them to the study and data collection procedures. At the start of data collection, flyers informing residents and family members about the study will be posted throughout the facility.

### **8.4.2 Intervention home Start-up**

Following randomization, the project director contacts the administrator of the intervention NH and informs them of their study assignment. She reminds him/her of the implications of the intervention assignment, asks him or her to select a site champion and facilitates completion of

the environmental scan questionnaire. Study start-up within intervention homes will involve at least 3 in-person meetings and up to weekly check-in phone calls between the research team PD and the site champion. During this time members of the TRAIN AD team will meet with members of the leadership team and site champion within the NH to review the program and intervention components and strategize about the best way to implement them within the NH. The following activities will occur during the 3 month planning period within intervention facilities:

1. Identify TRAIN-AD site champion
2. Completion of infection management questionnaire
3. Develop implementation plan with NH leadership during 3 on-site planning meetings
4. Identify targeted providers
5. Schedule training seminar
6. Provide orientation packages, conduct training seminars, and introduce on-line course to targeted providers
7. Conduct final facility set-up (e.g., hang posters of algorithms and study flyers throughout NH).

#### 8.4.2.1 Identification of site champion

At the start of the planning period, each NH will designate at least one champion. This individual needs to be someone engaged in infection management who understands the special concerns of advanced dementia residents. The site champion will most likely be either the DON, individual responsible for infection control, or nurse directing dementia care. The site champion will work with the research team throughout the planning and intervention period to facilitate successful program implementation. He or she serves as a primary contact for both providers within the NH and for the research team. Site champions are provided with a compendium of references and support tools at the start of the program and are encouraged to contact the project director with questions or concerns. Monthly phone conference huddles will be held when site champions from all intervention sites have the opportunity to discuss the program and provide suggestions/support to one another. The champion is an on-site leader and resource, working with both facility and research team to increase likelihood of program success. Site champions will:

- Help tailor TRAIN-AD to NH culture
- Identify and motivate providers
- Facilitate training seminars
- Review prescribing feedback reports
- Encourage infection management discussions in care planning
- Integrate program into quality improvement activities

#### 8.4.2.2 Development of implementation plan with NH leadership

Successful program planning and implementation depends on teamwork between members of the facility team and the research team. This starts with the 3 month planning period wherein the research team and NH team meet at least monthly to review and optimize plan for program roll-out. Throughout the program, the research team will work with members of the facility team to optimize the program within the facility and to support program activities within the facility.

#### 8.4.2.3 Identify targeted providers

See section 7.1.3 for description of provider eligibility criteria. Prior to the program's initial provider training seminar and every 6 months throughout the program (months 6,12, 18), the site champion will generate a list of providers with primary care responsibilities for residents with advanced dementia who will be targeted to complete the training seminar and on-line course

#### 8.4.2.4 Provide orientation packets, conduct training seminars, and introduce on-line course to targeted providers

Two weeks prior to all training seminars, the project director will send orientation packets to targeted providers. Each provider will be invited to attend one of the seminars where the TRAIN-AD program and components will be reviewed in detail. Providers will be asked to utilize reference materials and participate in the online course within one month of receiving the course invitation. Group seminars will be conducted at the NH twice the same day to reach various shifts. One on one sessions will be arranged for providers unable to attend the group training. The first training seminar marks the official start of the intervention period within each facility.

#### 8.4.2.5 Conduct final facility set-up (e.g., hang posters of algorithms and study flyers throughout NH).

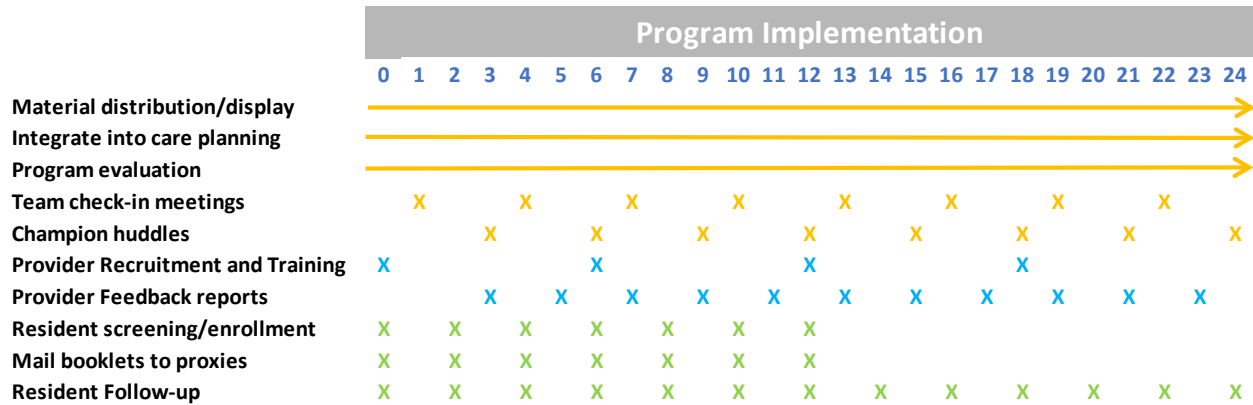
Immediately following initial training seminar, intervention materials will be posted and made available throughout the facility. The site champion will be asked to contact the research team for more materials as necessary throughout the intervention period.

### **8.5 On-going implementation**

Ongoing implementation will involve a number of procedures and strategies to support efforts within participating NHs and to encourage program success.

1. The research team and a trained physician will meet with the NH leadership every 6 months to review the overall project status, prescribing feedback, provider training and course completion, and proxy reaction to booklets. They will strategize about ways to further improve implementation.
2. On-site training seminars will be conducted by our team every 6 months to train newly hired providers, reinforce learning for on-going providers, and review cases to illustrate key points, and problem-solve ongoing concerns. (With time, the site champion will co-lead these sessions).
3. Prescribing feedback reports will be sent to the TRAIN-AD site champion and prescribing providers every 2 months.
4. The research team will facilitate huddles every quarter for site champions at multiple intervention facilities.
5. Study materials will be available and on display and resident charts will be reviewed every other month throughout the intervention period.

The chart below reflects the schedule of activities which occur during the 24-month implementation period at each NH:



### 8.5.1 Materials distributed/displayed throughout NH

Study materials will be posted and available throughout the intervention period. Research notice flyers and algorithm posters will remain posted throughout the intervention period. All other study materials will be available through the study site champion and research team upon request including: booklets, algorithms and communication guidance cards

### 8.5.2 Integration into care planning practices

During the provider training seminar and throughout the intervention period, direct care providers are encouraged to include infection management in quarterly care planning meetings. In the letter accompanying the booklet at the time of mailing, proxies are encouraged to discuss the booklet with their providers.

### 8.5.3 Program Evaluation

Throughout the intervention period, program implementation success will be monitored. By the following metrics: i. the proportion of targeted providers who attended an initial training session, ii. the proportion of targeted providers who completed the online course, and iii. rate of suspected UTIs and LRIs treated when minimal criteria not present as measured by the q2month prescribing provider feedback reports. The project director will also regularly (*see section 8.5.4*) with the site champion to review the project’s status, problem solve any issues, and adapt the program as needed. The research team encourages the NH leadership team and site champion to include the TRAIN-AD program in their quality improvement initiatives.

### 8.5.4 Team check-in meetings

Throughout the intervention period, the research PD will engage the champion in periodic check-in meetings to address questions or issues that arise. The PD will make monthly phone calls and schedule on-site meetings with champion and members of the leadership team every 6 months or as desired to review program progress, and address questions and concerns as they arise throughout the trial.

### 8.5.5 Provider recruitment and training

Provider identification and recruitment efforts will be ongoing throughout the intervention

period. Training seminars and invitations to the online course will be conducted at the start of the intervention and again at months 6, 12 and 18.

#### 8.5.6 Provider feedback reports

Every 2 months, starting in month 3, site champions and providers will be sent (mail/email) reports with aggregated facility data. Each provider will receive their own data.

#### 8.5.7 Resident screening and enrollment

Bi-screening eligibility screening and enrollment of new residents will be ongoing for the first 12 months in each participating facility.

#### 8.5.8 Mail booklet to proxies

Within one week of every bimonthly resident eligibility screening, the project director facilitates the mailing of study information and the infection management booklets to the proxies of eligible residents. The mailing includes research team contact information for the proxy to use to request exclusion from the study and is accompanied by a letter from the site champion explaining the contents and reason for the mailing. Following the 12 month enrollment period, proxies and providers can still obtain a copy of the booklets from the site champion or by request to the research team.

#### 8.5.9 Resident follow-up

Bimonthly chart reviews will be conducted for 12 months or until death for all enrolled residents.

#### 8.5.10 Quarterly site champion “huddles”

The research project director will facilitate monthly “huddles” via conference call for all active site champions. The huddles provide an opportunity for the champions to exchange ideas and experiences in their role and provide an opportunity for them to support and problem solve with other site champions

### **8.6 Concomitant Interventions**

Following randomization, but prior to initiation of intervention period, the PD conducts a structured survey with senior administrators in all control and intervention facilities to ascertain information the facility’s infection management activities, advance care planning practices, and palliative care/hospice services. Regardless of whether or not participating facilities engage in a separate antimicrobial stewardship programs during our intervention period, all randomized NHs will be retained in the analyses in accordance with intention-to-treat principles.

### **8.7 Intervention fidelity**

Our approach fidelity monitoring reflects an attempt to balance intervention adherence with a pragmatic approach to implementation. All targeted providers will be sent the orientation package (printed training material, laminated cards with algorithms), and be exposed to the algorithms posters strategically place in the NH. We will aim for >90% attendance of providers at either an initial group training group or 1:1 session and 70% completion of the on-line course.



Prescribing feedback reports will provide an on-going measure of adherence to the management algorithms.

## **9 DATA COLLECTION ELEMENTS AND PROTOCOL**

### **9.1 Facility Data**

Nursing home data are collected prior to the start of the study for descriptive purposes and to inform the development of a list of eligible nursing homes for recruitment. Prior to recruitment efforts, NH characteristics that may be relevant to advanced dementia care, were abstracted from the Medicare Nursing Home Compare, including: the number of beds, hospital-based, special care dementia unit, nursing and nursing assistant hours/resident/day, and number of deficiencies on state inspections. Long-term Care: Facts on Care in the US (<http://www.ltcfocus.org/>) is also used to gather information about potentially eligible NHs that will help balance factors for the randomization procedures (see SAP), including number of beds, number of residents with advanced cognitive impairment, and number of Black residents. Administrators of participating facilities are also asked whether NPs/PAs are on staff and whether there is an open or closed medical staff. At the time of initial enrollment and every 12 months during the implementation period, following randomization, but prior to initiation of intervention period, the PD conducts a structured written survey with senior administrators in all control and intervention facilities to ascertain information the facility's infection management activities, advance care planning practices, and palliative care/hospice services.

### **9.2 Resident assessments**

Resident data will be collected by RAs masked to the study arms. All data will be obtained from the residents' charts except for functional status and proxy ability to communicate in English, which will be ascertained in a 1-minute nurse interview. Data is collected from the medical records of enrolled residents every 2 months for up to 12 months, unless the resident passes or the proxy requests to opt out during that time. Their charts are abstracted at baseline, q2months, and within 30 days of death to determine whether antimicrobials were prescribed. If a treated episode was a suspected LRI or UTI, documented signs/symptoms will be ascertained to assess whether minimal criteria to start antimicrobials were present. Procedures used to evaluate these episodes (chest x-rays, bladder catheterization, blood draws, hospital transfer), and documented advance care planning about infection management (provider/proxy discussions and advance directives to withhold antimicrobials) will also be collected. A 1-minute nurse interview at baseline will also be done to assess the resident's functional status.

Demographic: (baseline) age, gender, race, ethnicity, length of NH stay, residing in a special care dementia unit, and proxy contact information (for mailing booklet) and relationship to resident.

Medical co-morbidity: (baseline) All active medical diagnoses.

Functional status: (baseline; nurse) Bedford Alzheimer's Nursing Severity-Subscale (BANS range, 7-28; higher score worse disability)

Antimicrobial exposure: (q2months, death) While analyses focus on treatment of suspected LRIs and UTIs, details about all antimicrobial courses will be ascertained from the medication administration records, including; suspected diagnoses, administration dates, agent, dose, route,

and prescribing provider. There are many ways to quantify antimicrobial exposure. We chose number of courses/person-years as our primary outcome as it best captures the intent of the intervention which is to reduce antimicrobial initiation. A course will be defined as starting an antimicrobial after a > 3-day treatment-free interval. Multiple antimicrobials given simultaneously for an episode will be considered single course for analytic purposes. For descriptive purposes, we will also quantify antimicrobial exposure as days of therapy (DOT)/person-days.

Treated suspected UTIs and LRIs: (q2months, death): Documented details will be collected for treated suspected UTIs and LRIs, including: i. vital signs, mental status changes, localized signs and symptoms (e.g., lung sounds, cough, hematuria), ii. procedures used to evaluate including bladder catheterizations, chest x-rays, blood draws, iii. hospital transfer (admission or emergency room (ER), and vi. treatment discussions between providers and proxies. Signs and symptoms will be used to determine whether minimal criteria to initiate antimicrobials were met as operationalized in SPREAD and the pilot study.

Advance care planning: (baseline, q2months, death). The occurrence and date of advance care planning events will be ascertained from all available documentation (e.g., progress notes physician orders, POLST forms) and will include: discussions between providers and proxies about infection management and new directives to withhold antimicrobials (intravenous, intramuscular and/or oral) will be ascertained. Do-not-resuscitate and do-not-hospitalize orders will also be collected for descriptive purposes.

Devices: (baseline, q2months, death) feeding tubes, foley catheters

Health services: (q2months, death) hospitalizations, emergency room visits, hospice enrollment. 3.C.vii.1.i.

Other major new acute illnesses: (q2months, death), e.g. fracture, stroke, seizures. Death: RAs will phone the NH (nursing units) q2month.

Death date will be obtained from the chart.

<b>Data Collection Elements and Protocol</b>			
<b>Data Collected</b>	<b>Purpose</b>	<b>From</b>	<b>When</b>
<b>Eligibility Screen</b>			
Age, length of NH stay, available proxy	Eligibility	Chart	Screen
Advanced dementia	Eligibility	Nurse, Chart	Screen
<b>IF ELIGIBLE</b>			
<b>Resident Characteristics</b>			
Demographic, medical comorbidity, functional status	Descriptive	Chart	Baseline
Antimicrobial exposure			
Total courses for LRIs and UTIs <sup>2</sup>	1 <sup>o</sup> Outcome (Aim 1)	Chart, MAR <sup>1</sup>	q2months, death
Total courses for LRIs and UTIs <sup>2</sup> not meeting minimal criteria	2 <sup>o</sup> Outcome (Aim 2)	Chart, MAR <sup>1</sup>	q2months, death
Burdensome procedures to evaluate suspected LRIs and UTIs	2 <sup>o</sup> Outcome (Aim 3)	Chart	q2months, death
Advance care planning	2 <sup>o</sup> Outcome (Aim 3)	Chart	Baseline, q2months, death
Devices	Descriptive	Chart	Baseline, q2months, death
Health services utilization, new acute illnesses	Descriptive	Chart	q2months, death
Death	Descriptive	Nurse, chart	Death
<b>Facility Characteristics</b>			
	Descriptive	NH Compare Administrator	Baseline Baseline, q12 months

<sup>1</sup>MAR=Medication Administration Record; <sup>2</sup>LRIs and UTIs= lower respiratory tract infections, urinary tract infections

### 9.2.1 Consenting Procedure (also see sections 7 and 16.2)

In accordance with federal guidelines, the HSL IRB granted a waiver of informed consent for the participation of both providers and residents (i.e., from proxies) based on: i. The determination of minimal risk, ii. The trial could not be practically conducted without the waiver. The NH is the unit of randomization and the intervention will be implemented as a new program for all advanced dementia residents. Including all eligible residents (versus only those consenting) reflects how the intervention would be used in the “real-world,” thus enhances the trial’s generalizability and interpretability, and iii. The trial does not adversely affect the rights and welfare of the subjects. Providers and proxies will have the opportunity to opt out at the start and throughout the implementation period, as described in Section 7.

### 9.2.2 Baseline Assessments

The charts of all eligible residents will be including in the baseline data abstraction unless the proxy has contacted the study team with a request for exclusion. Baseline assessments are chart review and data extraction along with a 1 minutes Bedford Alzheimer’s Nursing Severity-Subscale (BANS) interview to assess residents functional status. Baseline assessment includes the following:

- Demographics
- Health status
- Chronic or co-morbidities
- Advanced directives
- Recent history of treatments or investigations
- Healthcare utilization
- BANS interview
- Infection Screen

### 9.2.3 Follow-up Visits

Follow up chart reviews will be completed every 2 months for up to 1 year or until the resident dies. If the resident dies during the 12 month follow up period, a post-death chart review will be conducted. Follow-up chart reviews include the following elements:

- Demographics
- Advance directives
- Treatments/Investigations
- Healthcare utilization
- Sentinel Events
- Infection Screen

### 9.2.4 Post death Chart review

Post death chart reviews will be conducted within 30 days of enrolled residents passing. The research nurse will access the residents chart in the same way as she did for follow up chart reviews and collect the following information:

- Advance directives
- Treatments/Investigations
- Healthcare utilization
- Sentinel events
- Infection Screen

## **10 HUMAN SUBJECT PROTECTIONS**

### **10.1 Sources of Data**

Residents' NH record: The residents' medical record containing information collected for routine clinical care will be abstracted at the baseline, q 2month and death assessments for up to 12 months. The following information will be obtained from the chart: demographic information, antimicrobial exposure and prescribing provider, lower respiratory and urinary tract episodes, medical comorbidity, advance care planning, devices, health care utilization, acute medical illnesses, and death date.

Nurse interviews: During screening procedures, nurses will be asked to identify subjects who meet criteria for Global Deterioration Stage 7. For enrolled residents, at baseline only, nurses will be asked to rate the functional status of the patients using the Bedford Alzheimer's Nursing Severity-Subscale during a 1-minute interview.

On-line course: Individual provider completion of the on-line course will be tracked.

NH residents, proxies, and NH providers (intervention arm only) will be assigned a study number known only to the co-principal investigators (PIs) and research assistants (RAs). NH providers in the intervention arm will be given a unique username and password to access the on-line education course known only to them, the PIs and project director. All documentation will

be stored in a locked area, accessible only to the PIs, RAs, and data manager. Data will be stored on computer workstations, accessible only through use of a unique password. Access to these data will be limited to study personnel on a “need to know” basis.

## **11 POTENTIAL RISKS OF STUDY PROCEDURES**

The study meets criteria for minimal risk. All the resident data will be obtained from their medical record and nursing interviews, and coded at the time of data entry to protect their confidentiality. The residents in the control NHs will receive usual care for suspected infections. Residents in the intervention arm will receive care for the suspected infections at the discretion of their primary care providers as guided by the practice intervention. Given that the intervention is based on consensus, peer reviewed guidelines, the risk from the intervention with regards to infection management is minimal.

### **11.1 Potential Medial Risk to Study Participants**

Patients with advanced dementia are very frail. In the natural course of the disease, we expect of 40% mortality rate over one year. Thus, while deaths will be reported to the Data Safety Monitor, they are not considered an adverse event. The intervention does not involve any direct treatment of residents. Treatment of suspected infections is ultimately at the discretion of the nursing home primary care provider. Nonetheless, as part of this study, every 2 months, we will be collecting data from the residents’ charts about the rates of suspected urinary and respiratory infections, treatment of these infections, and appropriateness of that treatments as defined by our primary outcome.

### **11.2 Potential psychosocial (non-medical) risks, discomforts, inconveniences of study procedures**

We do not anticipate any potential psycho-social risks discomforts or inconveniences of study procedures beyond those encountered in usual care practices. The intervention provides information for proxies about infections in advanced dementia residents to promote informed decision-making that it is concordant with preferences, which is also desired goal for high quality nursing home care. The intervention was very well-received with no adverse events in the pilot study. Thus, we believe the intervention does not incur any greater distress than usual practice. Second, data collection conforms to the definition of minimal risk. No direct input from the residents or proxies is needed to complete any data for this study. All resident data are already being collected as part of routine medical care with the exception of the 1-minute nursing interview at baseline to quantify the resident’s functional status for descriptive purposes. All resident data are entered into a password protected encrypted software system using unique study identifiers. The data sheet linking residents with unique study ids is maintained in a separate secure system location at the discretion of the study site champion.

One additional potential burden of this study is the time commitment of the NH staff to assist with eligible subject identification, which involves 1-minute baseline nursing interviews, and intervention implementation. We will make every effort to minimize staff burden. Staff at the ~60 facilities that have participated in our prior large studies that used similar methods to recruit residents with advanced dementia felt the procedures were not too onerous. Based on our experience, the baseline nursing interview to quantify functional status is expected to take ~1

minute to complete. It is unlikely this burden will fall on a single nurse. Every effort will be made to conduct these interviews at times that are convenient for the nurses. Some burden will be experienced by the TRAIN-AD site champion and 15-20 targeted providers/NH (12-16 nurses, 1-3 physicians, 0-3 NPs/PAs) in the 12 intervention NHs with respect to the time required for initial training, completion of the on-line education course, use of algorithms to guide antimicrobial initiation, and review of prescribing feedback reports. All training procedures will be done at the convenience of these providers. Their involvement is voluntary. Group seminars will be conducted twice the same day to reach various shifts, and 1:1 sessions will be arranged for providers unable to attend the group training. The on-line course can also be done at the providers' convenience.

### **11.3 Adverse Events and Serious Adverse Events**

The study intervention is a facility level training and educational program in line with CDC recommendations for infection management and antimicrobial stewardship programming. The research team has no direct contact with study participants. We do not anticipate any serious adverse events or adverse events to occur in this study.

### **11.4 Reporting Procedures**

Although, there are no anticipated adverse events, should any unanticipated study-related event of concern come to the attention of any research team member (i.e., report by site champion, proxy or provider), it will be documented on a 'event of concern' form by the PD and reviewed within 24 hours with the PI. Site champions will be trained on this procedure during the 3-month facility planning period. Any unanticipated adverse event will be promptly reported in writing to the NIH and the HSL IRB within 48 hours by the PI.

### **11.5 Follow-up for Adverse Events:**

If an adverse event was deemed to have occurred, the site champion will be instructed to check on the provider/family/resident who experienced the event within 24 hours of the event to see how he/she is managing. If deemed necessary, the individual will be referred to the appropriate health care professional based on the nature of the event (i.e, counseling with a NH social worker, medical attention by a physician). In the case of a provider or family member, if deemed necessary, the site champion may suggest to the proxy that he/she contact his/her own primary care provider. The research project director will contact the facility site champion within 48 hours of the event to determine the status of the provider/family/resident and whether further follow-up was deemed necessary. The project director will report the follow-up information to the PI (by telephone) and to the data safety monitor (in writing) within 72 hours.

### **11.6 Safety Monitoring**

As agreed upon by the NIA and overseeing project officer, Dr. Marcel Salive, safety monitoring will be the responsibility of a Data Safety Monitor (DSM), Dr. David Mehr of the University of Missouri. The PI will meet with Dr. Mehr during the preparation stage of the study via conference call, to provide input and guidance on the study evaluation and intervention protocols, data handling activities, and quality assurance and safety issues. Together they will agree on definitions of an adverse event and the content of the regular DSM reports. Once the study starts, the DSM will be sent a report prepared by the research team summarizing the

overall study status, recruitment, data completion rates, adverse events, protocol deviations, and outcomes (if desired). Data will be presented aggregated for both arms of the RCT, and in a sub-report that the PI will not see, in a semi-blinded fashion with study arms labeled as Group 1 and Group 2. The DSM will be free to determine the need to stop the continuation of the study based on examination of these reports.

## **12 INTERVENTION DISCONTINUATION**

The study may be discontinued at any time by the IRB, the NIA, OHRP or other government agencies as part of their duties to ensure that research participants are protected. Individual NHs in the intervention arm may withdraw from study participation at any time at the discretion of their senior management or corporate supervisors. Providers can opt out of any part of intervention participation at any time, and while not being asked to provide informed consent for this research, resident proxies can opt out of reading the infection management booklet and contact the research team at any time to request exclusion of their resident from ongoing data collection efforts. Program being adopted into the clinical practice of participating intervention NHs. Such refusals are expected as part of this pragmatic trial.

## **13 STATISTICAL CONSIDERATIONS (SEE SAP)**

### **DATA COLLECTION AND QUALITY ASSURANCE**

#### **13.1 Data Use Agreements**

There are no Data Use Agreement (DUA) for this study. All facility level data comes from public data sources and all resident data is obtained from residents' medical charts, with the exception of a 1-minute nurse interview at baseline to assess the resident's functional status.

##### **13.1.1 Residents:**

Data will be collected by a trained RAs masked to the aims, outcomes, and that there are 2 arms. All data will be obtained from the residents' charts except for functional status and proxy ability to communicate in English, which will be ascertained in a 1-minute nurse interview at baseline. Charts will be abstracted (~20 minutes) when residents are first enrolled (baseline), q2months, and within 30 days of death, for up to 12 months. REDcap will be used for collecting data electronically and tracking protocol elements.

All resident data will be entered and managed in HSL data systems under a confidential study ID. The code sheet linking study ID to individual resident will be kept in a secure location within the NH. HSL data bases will maintain data under subject study ID related to nursing home name, age, and gender. Access to this code sheet will be limited to the RA assigning the codes, the study site champion and the project manager as needed to facilitate mailing of booklets to proxies of enrolled residents.

##### **13.1.2 Proxies**

Proxy information is collected to facilitate mailing of the infection management booklet and study information. Information collected is limited to name and mailing address which is abstracted from the resident's chart, and the proxy's ability to communicate in English, which is obtained from the unit nurses. All proxy information will be maintained in the secure study

subject code sheet maintained within the NHs.

## **13.2 Identifiers to be stored separately from resident data**

### **13.2.1 Key or link to the codes**

A code sheet linking individual residents and proxy information with the assigned study IDs will be kept in hard copy and/or electronic format on a password protected flash drive in a secure location within the participating NH. The location and means of securing this data will be decided in collaboration with the NH leadership team and study champion.

#### **13.2.1.1 Individuals (or study roles) who will have access to identifiable data, or key/link to codes**

Research assistants who will be conducting eligibility screenings and subsequent chart reviews, study site champions, and project directors who will be sending the proxy materials from within the nursing home have access to the study ID code sheet.

## **13.3 Data security measures**

All access to data is restricted to those in the research group who have been authorized by the PI to utilize this information. Because HSL is a licensed hospital, the information technology group adheres to all the policies and practices under the HIPAA regulations. Although not required, HSL treats all lines of business as HIPAA locations and hold them accountable to these security standards therefore, creating a very tight computing environment. In order to preserve confidentiality, subjects will be assigned a study number known only to the co-PIs, PDs, RAs and data manager. A code sheet linking individual residents and proxy information with the assigned study IDs will be kept in hard copy and/or electronic format on a password protected flash drive in a secure location within the participating NH.

All data collected electronically by RAs on laptop computer using internet-based electronic data capture programs (i.e., REDcap) accessible only to research personnel through the use of unique password. All written documentation with subject information will be stored in a locked area within the nursing home, accessible only to the RAs, PDs, and site champion. All data will be stored on computer workstations, accessible only through use of a unique password. Access to these data will be limited to study personnel on a “need to know” basis. If a NH resident is deemed ineligible for the study, all personal health information obtained for screening purposes will be destroyed as soon as possible.

#### **13.3.1 Timing of destruction of materials containing identifiers and keys/links to codes**

Once the study has ended and all subjects have been followed for safety and study outcomes.

#### **13.3.2 Method for destroying materials with identifiers and keys/links to codes**

Paper documents will be shredded and electronic files will be deleted.

## **13.4 Data Collection Forms**

There are three levels of data collection. Data are collected at the start of the study and annually thereafter from NH leadership related to the site’s independent infection management initiatives and readiness for infection management program implementation. Resident level data are



collected at baseline and every 2 months for 12 months or until the resident deceases. Provider level data are collected via site champion interaction and from their participation in the HMS online course. Finally, proxy name and mailing address is obtained from the resident's chart during eligibility screening.

#### 13.4.1 Facility level data collection

General facility information including its size, address, for-profit status, acuity status and demographic data is obtained from public data sources including Medicare Nursing Home Compare and LTCfocus. Facility level data collection will be conducted by the research team in an effort to ascertain potential concomitant initiatives and to assess readiness for new program implementation. This questionnaire has been built into the Redcap data project and conducted prior to program planning efforts within the facility and annually thereafter.

#### 13.4.2 Resident Data collection forms

The following data collection forms, programed into redcap are used for resident-level data collection:

- Resident eligibility screening
- Baseline resident chart review
- Resident bimonthly chart reviews
- Post Death Chart review
- Infection Screening (occurs at baseline and bimonthly chart reviews)
- UTI and LRI infection modules (used when either UTI or LRI are recorded during an infection screening)

#### 13.4.3 Provider level data collection

Provider names and contact information will be obtained by the research project director from the site champion. Data related to their participation in the online course will be obtained from HMS website. This data will include the provider results on the pre and post-test and course completion status. Data will be uploaded and maintained in a REDap provider database maintained by the project manager within IFAR. Access to this data will be limited to the project director and study data analyst in blinded form.

### **13.5 Data Management**

Data management and analysis for the study will take place at HSL under the direction of the informatics and biostatistics cores at the Institute for Aging Research (IFAR). All access to data is restricted to those on the research team who have been authorized by the PI to use this information. The HSL information technology (IT) department adheres to all the policies and practices under HIPAA regulations and is responsible for securing IFAR's IT infrastructure including physical servers and application software. IFAR has established additional sensitive data policies and procedures in concert with the IRB to ensure safe data handling by faculty and staff.

### 13.5.1 Resident/Proxy data collection

One to two research assistants (RAs) will be responsible for screening subjects and conducting chart reviews. To the extent possible, the RAs collecting outcome data through chart reviews and follow-up proxy interviews will be blinded to nursing home randomization. All data will be collected and entered electronically by the RAs using laptop computers in the field. State-of-the-art electronic data capture software and programming (e.g., REDCap) will be used for these purposes. Once entered, the data will be downloaded and entered into the computer systems at HSL IFAR for cleaning, programming and analyses.

### 13.5.2 Provider data collection and management

The pre/post knowledge scores of providers doing the education modules in intervention NHs will be submitted to the research team by the staff at the HMS CME office using a password protected electronic computer file. Once received, HSL data management will strip the scores of subject identifiers and enter the data into the electronic data file.

## **13.6 Quality Assurance**

### 13.6.1 Training

All research staff have been trained in human subject safety and data security measures. SOPs document procedural requirements for all study related activities. Each member of the research team is trained in their research role by the PI and PDs in accordance to the SOP. Cross training among the research team ensures redundancy within the team to ensure uninterrupted procedures throughout the trial.

### 13.6.2 Protocol Deviations

All identified protocol procedures will be tracked in a protocol deviations database by the project director and included in periodic reports to the data safety monitor for review.

### 13.6.3 Monitoring

The TRAIN-AD program is designed to be adapted to optimize implementation within each participating NH. A few essential elements will be monitored by the research team during periodic site visits and implementation check-in meetings with the site champions. Essential components include the visible display of study flyers and infection management guidelines throughout the facility. Additionally, the PD will ensure, through ongoing interactions with the site champion that all new providers are invited to participate in the on-site trainings and online course. The RA conducting the periodic chart review will ensure that the procedures for maintaining securing around the participant code sheet are being followed within the facility. The PD will conduct monthly reviews of data collection to ensure that all targeted data collection is completed in a timely manner.

## **14 PARTICIPANT RIGHTS AND CONFIDENTIALITY**

### **14.1 Institutional Review Board (IRB) Review**

This protocol and the informed consent and HIPAA waiver applications have been reviewed and

approved by Hebrew Senior Life's IRB. Continuation of study is contingent on annual review and approval by the IRB. Any changes to study protocol or materials will be submitted to the IRB for review and approval prior to implementation.

## 14.2 Informed Consent Forms

A waiver of informed consent and HIPAA Waiver of Patient Authorization was approved by the NIH, and Hebrew Senior Life's Institutional Review Board, based on federal guidelines 45 CFR 46.116(d):

1. The research involves no more than minimal risk to the participants;
2. The waiver or alteration will not adversely affect the rights and welfare of the participants;
3. The research could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

### 14.2.1 The study meets criteria for minimal risk as per HHS 45 CFR 45.102:

“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Explanation

**First**, TRAIN-AD is an education and training program rolled out at the facility level which promotes the general recommendations of the Center for Disease Control (CDC) that NHs engage in antimicrobial stewardship activities as a standard of care. The educational content of the program is aligned with CDC recommendations for antimicrobial prescribing based on national consensus guidelines, intended to improve infection management for residents with advanced dementia. The program also provides information for proxies about infections in advanced dementia residents to promote informed decision-making that is patient-centered and consistent with goals for patient care. At no point will members of the research team have direct contact with residents or proxies or directly affect care.

**Second**, data collection conforms to the definition of minimal risk. Data collected for research purposes will be obtained through bimonthly review and abstraction from the charts of enrolled residents and a single 1-minute nursing interview at baseline to quantify the resident's functional status for descriptive purposes. Research data will be maintained in an encrypted, password protected database which uses unique study IDs for all enrolled residents and proxies. The code sheet linking study subjects with study IDs will be kept in a secure location within the participating NH.

### 14.2.2 The waiver or alteration will not adversely affect the rights and welfare of participants

Explanation

TRAIN-AD is a facility-wide education and training program that promotes CDC established best practices for infection management and CMS recommendations for antimicrobial stewardship within nursing homes. The program promotes the provision of patient-centered care in an effort to improve care quality, but individual treatment decisions remain entirely at the discretion of the residents' medical providers. Research team members have no direct contact

with residents or proxies and all. With the exception of the 1-minute nurse interview to characterize functional status, all resident data will be obtained from residents' existing medical record, and recorded in the secure research database using unique study identifiers. Study information is mailed to proxies of eligible residents and posted throughout the facility. Residents' healthcare proxies can opt-out of allowing the research team to include resident data in the study at any time.

#### 14.2.3 The research could not practicably be carried out without the waiver or alteration

##### Explanation

Obtaining individual informed consent for this study is impractical for this facility-level education and training program, which involves no direct contact by our research team with either residents or proxies and leaves resident care decisions entirely at the discretion of the providers. The intervention is being rolled-out facility-wide, so all residents with advanced dementia within the facility are potentially affected by the program. The waiver of consent enables us to assess the effect of the intervention as it is implemented in the real world.

#### 14.2.4 Whenever appropriate, the participants will be provided with additional pertinent information after participation:

Upon the study's conclusion, results and publications will be provided by the research team to the NH administrators and providers, as well as proxies of residents with advanced dementia, as requested.

### 14.3 Participant Confidentiality

This trial has been granted a HIPAA Waiver of Requirement for Authorization for Release of Protected Health Information for Research Purposes from the Hebrew Senior Life IRB. In order to preserve confidentiality, subjects will be assigned a study number known only to the RAs PDs and site champions. All physical documentation and IT assets are stored in a locked areas within the participating NHs and within HSL, monitored 24-hours a day by security personnel, and accessible only by authorized employees. Access to the HSL cooperate computer network is strictly prohibited and all electronic research data will be stored on dedicated IFAR systems located on our private network. Access to these data will be limited to study personnel on a "need to know" basis. If a NH resident is deemed ineligible for the study, all personal health information obtained for screening purposes will be destroyed as soon as possible.

## 15 STUDY DISCONTINUATION

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

## 16 ETHICAL CONSIDERATIONS

Ethical consideration for the PROVEN trial will be in *accordance* with the Federal Policy for the Protection of Human Subjects (HHS Human Subjects Research 45 Code of Federal Regulations (CFR) 46).

## 17 COMMITTEES

Purpose	Meeting Chair	Attendees	Frequency	Timing
Executive committee	Mitchell	Mitchell, D'Agata, Bergman, Carroll	Q2weeks	Months 1-52
Data Safety Monitoring	Mitchell	Mitchell, Shaffer, Habtemariam, Tsai, Bergman and Mehr	Q6 Months	
Full team meetings	Co-led	Mitchell, D'Agata, Shaffer, Hanson, Bergman, Anderson (months 1-24 only), Carroll, Habtemariam, Tsai, Loizeau	Quarterly	Months 1-52
Field operations	Co-led	Mitchell, D'Agata, Carroll, Bergman	Weekly Q2weeks	Months 1-20 Months 20-38
Intervention content and Implementation	D'Agata	D'Agata, Mitchell (only meeting that do not require naming of facilities), Carroll, Bergman, Loizeau, Anderson (ad hoc basis)son <sup>1,3</sup>	Weekly Q2weeks	Months 1-20 Months 20-38
Data management/analyses	Mitchell	Mitchell, Bergman, Habtemariam, Tsai, Shaffer <sup>1</sup>	Monthly Weekly	Months 7-44 Months 45-52

## 18 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

## 19 REFERENCES

### Bibliography

1. Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-38.
2. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003;60:1119-22.
3. Goldfeld KS, Stevenson DG, Hamel MB, Mitchell SL. Medicare expenditures among nursing home residents with advanced dementia. *Arch Intern Med* 2011;171:824-30.
4. Wimo A, Ljunggren G, Winblad B. Costs of dementia and dementia care: a review. *Int J Geriatr Psychiatry* 1997;12:841-56.
5. Deaths: Leading Causes for 2011. National Vital Statistics Reports, 2015. (Accessed August 12, 2015, at [http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64\\_07.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_07.pdf).)
6. Givens JL, Jones RN, Shaffer ML, Kiely DK, Mitchell SL. Survival and comfort after treatment of pneumonia in advanced dementia. *Arch Intern Med* 2010;170:1102-7.
7. Volicer L. Management of severe Alzheimer's disease and end-of-life issues. *Clin Geriatr Med* 2001;17:377-91.
8. Chen JH, Lamberg JL, Chen YC, et al. Occurrence and treatment of suspected pneumonia in long-term care residents dying with advanced dementia. *J Am Geriatr Soc* 2006;54:290-5.
9. Mitchell SL, Shaffer ML, Loeb MB, et al. Infection management and multidrug-resistant organisms in nursing home residents with advanced dementia. *JAMA Intern Med* 2014;174:1660-7.
10. Mody L. Optimizing antimicrobial use in nursing homes: no longer optional. *J Am Geriatr Soc* 2007;55:1301-2.
11. Norman DC. Management of antibiotic-resistant bacteria. *J Am Geriatr Soc* 2002;50:S242-6.
12. Loeb M, Simor AE, Landry L, et al. Antibiotic use in Ontario facilities that provide chronic care. *J Gen Intern Med* 2001;16:376-83.
13. Loeb M, Brazil K, Lohfeld L, et al. Optimizing antibiotics in residents of nursing homes: protocol of a randomized trial. *BMC Health Serv Res* 2002;2:17.
14. Yoshikawa TT. Resistant pathogens: considerations in geriatrics and infectious disease. *J Am Geriatr Soc* 2002;50:S225.
15. Pickering TD, Gurwitz JH, Zaleznik D, Noonan JP, Avorn J. The appropriateness of oral fluoroquinolone-prescribing in the long-term care setting. *J Am Geriatr Soc* 1994;42:28-32.
16. Yoshikawa TT. Antimicrobial resistance and aging: beginning of the end of the antibiotic era? *J Am Geriatr Soc* 2002;50:S226-9.
17. Pop-Vicas A, Mitchell SL, Kandel R, Schreiber R, D'Agata EM. Multidrug-resistant gram-negative bacteria in a long-term care facility: prevalence and risk factors. *J Am Geriatr Soc* 2008;56:1276-80.
18. The Core Elements of Antibiotic Stewardship for Nursing Homes. Centers for Disease Control and Prevention, 2015. (Accessed September 21, 2015, at <http://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html>.)
19. Daneman N, Bronskill SE, Gruneir A, et al. Variability in Antibiotic Use Across Nursing Homes and the Risk of Antibiotic-Related Adverse Outcomes for Individual Residents. *JAMA Intern Med* 2015;175:1331-9.

20. Yates E, Mitchell SL, Habtemariam D, Dufour AB, Givens JL. Interventions Associated with the Management of Suspected Infections in Advanced Dementia. *J Pain Symptom Manage* 2015.
21. Dufour AB, Shaffer ML, D'Agata EMC, Habtemariam D, Mitchell SL. Survival after Suspected Urinary Tract Infections in Advanced Dementia. *J Am Geriatr Soc* 2015;doi: 10.1111/jgs.13833.
22. Mitchell SL, Shaffer ML, Kiely DK, Givens JL, D'Agata E. The study of pathogen resistance and antimicrobial use in dementia: study design and methodology. *Arch Gerontol Geriatr* 2013;56:16-22.
23. Loeb M, Bentley DW, Bradley S, et al. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. *Infect Control Hosp Epidemiol* 2001;22:120-4.
24. Crnich CJ, Jump R, Trautner B, Sloane PD, Mody L. Optimizing Antibiotic Stewardship in Nursing Homes: A Narrative Review and Recommendations for Improvement. *Drugs Aging* 2015;32:699-716.
25. Inside NIA: A Blog for Researchers. A special budget for Alzheimer's and related dementias 2016. (Accessed August 10, 2015, at <<https://www.nia.nih.gov/research/blog/2015/08/special-budget-alzheimers-and-related-dementias>>.)
26. Dying In America: Improving Quality and Honoring Individual Preferences Near the End-of-Life. In: Institute of Medicine of the National Academies; 2014.
27. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. (Accessed August 24, 2015, at [https://www.alz.org/facts/downloads/facts\\_figures\\_2015.pdf](https://www.alz.org/facts/downloads/facts_figures_2015.pdf).)
28. Mitchell SL, Teno JM, Miller SC, Mor V. A national study of the location of death for older persons with dementia. *J Am Geriatr Soc* 2005;53:299-305.
29. Ahronheim JC, Morrison RS, Morris J, Baskin S, Meier DE. Palliative care in advanced dementia: a randomized controlled trial and descriptive analysis. *J Palliat Med* 2000;3:265-73.
30. Mitchell SL, Kiely DK, Hamel MB. Dying with advanced dementia in the nursing home. *Arch Intern Med* 2004;164:321-6.
31. Mitchell SL, Black BS, Ersek E, et al. Advanced dementia: State-of-the-art and priorities for the next decade. *Ann Intern Med* 2012;In press.
32. Mitchell SL. CLINICAL PRACTICE. Advanced Dementia. *N Engl J Med* 2015;372:2533-40.
33. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139:1136-9.
34. Morrison RS, Siu AL. Survival in end-stage dementia following acute illness. *JAMA* 2000;284:47-52.
35. Mehr DR, van der Steen JT, Kruse RL, Ooms ME, Rantz M, Ribbe MW. Lower respiratory infections in nursing home residents with dementia: a tale of two countries. *Gerontologist* 2003;43 Spec No 2:85-93.
36. van der Steen JT, Kruse RL, Ooms ME, et al. Treatment of nursing home residents with dementia and lower respiratory tract infection in the United States and The Netherlands: an ocean apart. *J Am Geriatr Soc* 2004;52:691-9.
37. D'Agata E, Mitchell SL. Patterns of antimicrobial use among nursing home residents with advanced dementia. *Arch Intern Med* 2008;168:357-62.
38. D'Agata E, Loeb MB, Mitchell SL. Challenges in assessing nursing home residents with advanced dementia for suspected urinary tract infections. *J Am Geriatr Soc* 2013;61:62-6.
39. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *Jama* 2007;298:1763-71.
40. Campaign to Reduce Antimicrobial in Healthcare Settings. 2007. (Accessed January 7, 2008, 2008, at <http://www.cdc.gov/drugresistance/healthcare/>.)

41. The Problem of Antimicrobial Resistance. 2006. (Accessed January 7, 2008, at <http://www.niaid.nih.gov/factsheets/antimicro.htm>.)
42. Kunin CM. Resistance to antimicrobial drugs--a worldwide calamity. *Ann Intern Med* 1993;118:557-61.
43. Holmberg SD, Solomon SL, Blake PA. Health and economic impacts of antimicrobial resistance. *Rev Infect Dis* 1987;9:1065-78.
44. Dommeti P, Wang L, Flannery EL, Symons K, Mody L. Patterns of ciprofloxacin-resistant gram-negative bacteria colonization in nursing home residents. *Infect Control Hosp Epidemiol* 2011;32:177-80.
45. Mody L, Gibson KE, Horcher A, et al. Prevalence of and Risk Factors for Multidrug-Resistant *Acinetobacter baumannii* Colonization Among High-Risk Nursing Home Residents. *Infect Control Hosp Epidemiol* 2015:1-8.
46. Mody L, Krein SL, Saint S, et al. A targeted infection prevention intervention in nursing home residents with indwelling devices: a randomized clinical trial. *JAMA Intern Med* 2015;175:714-23.
47. Cassone M, Mody L. Colonization with Multi-Drug Resistant Organisms in Nursing Homes: Scope, Importance, and Management. *Curr Geriatr Rep* 2015;4:87-95.
48. Toubes E, Singh K, Yin D, et al. Risk factors for antibiotic-resistant infection and treatment outcomes among hospitalized patients transferred from long-term care facilities: does antimicrobial choice make a difference? *Clin Infect Dis* 2003;36:724-30.
49. Trick WE, Weinstein RA, DeMarais PL, et al. Colonization of skilled-care facility residents with antimicrobial-resistant pathogens. *J Am Geriatr Soc* 2001;49:270-6.
50. Niclaes L, Buntinx F, Banuro F, Lesaffre E, Heyrman J. Consequences of MRSA carriage in nursing home residents. *Epidemiol Infect* 1999;122:235-9.
51. Suetens C, Niclaes L, Jans B, et al. Methicillin-resistant *Staphylococcus aureus* colonization is associated with higher mortality in nursing home residents with impaired cognitive status. *J Am Geriatr Soc* 2006;54:1854-60.
52. Tacconelli E, Pop-Vicas AE, D'Agata EM. Increased mortality among elderly patients with methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Hosp Infect* 2006;64:251-6.
53. Wiener J, Quinn JP, Bradford PA, et al. Multiple antibiotic-resistant *Klebsiella* and *Escherichia coli* in nursing homes. *JAMA* 1999;281:517-23.
54. Capitano B, Leshem OA, Nightingale CH, Nicolau DP. Cost effect of managing methicillin-resistant *Staphylococcus aureus* in a long-term care facility. *J Am Geriatr Soc* 2003;51:10-6.
55. Manzur A, Vidal M, Pujol M, et al. Predictive factors of methicillin resistance among patients with *Staphylococcus aureus* bloodstream infections at hospital admission. *J Hosp Infect* 2007;66:135-41.
56. Wright SW, Wrenn KD, Haynes M, Haas DW. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. *Am J Emerg Med* 2000;18:143-6.
57. Pop-Vicas AE, D'Agata EM. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. *Clin Infect Dis* 2005;40:1792-8.
58. Mody L, Bradley SF, Strausbaugh LJ, Muder RR. Prevalence of ceftriaxone- and ceftazidime-resistant gram-negative bacteria in long-term-care facilities. *Infect Control Hosp Epidemiol* 2001;22:193-4.
59. Lee DC, Barlas D, Ryan JG, Ward MF, Sama AE, Farber BF. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: prevalence and predictors of colonization in patients presenting to the emergency department from nursing homes. *J Am Geriatr Soc* 2002;50:1463-5.
60. Suetens C, Niclaes L, Jans B, et al. Determinants of methicillin-resistant *Staphylococcus aureus* carriage in nursing homes. *Age Ageing* 2007;36:327-30.
61. Loeb MB, Craven S, McGeer AJ, et al. Risk factors for resistance to antimicrobial agents among nursing home residents. *Am J Epidemiol* 2003;157:40-7.



62. Sandoval C, Walter SD, McGeer A, et al. Nursing home residents and Enterobacteriaceae resistant to third-generation cephalosporins. *Emerg Infect Dis* 2004;10:1050-5.
63. Bonomo RA. Multiple antibiotic-resistant bacteria in long-term-care facilities: An emerging problem in the practice of infectious diseases. *Clin Infect Dis* 2000;31:1414-22.
64. Muder RR, Brennen C, Drenning SD, Stout JE, Wagener MM. Multiply antibiotic-resistant gram-negative bacilli in a long-term-care facility: a case-control study of patient risk factors and prior antibiotic use. *Infect Control Hosp Epidemiol* 1997;18:809-13.
65. Fabiszewski KJ, Volicer B, Volicer L. Effect of antibiotic treatment on outcome of fevers in institutionalized Alzheimer patients. *JAMA* 1990;263:3168-72.
66. van der Steen JT, Ooms ME, Ader HJ, Ribbe MW, van der Wal G. Withholding antibiotic treatment in pneumonia patients with dementia: a quantitative observational study. *Arch Intern Med* 2002;162:1753-60.
67. van der Steen JT, Ooms ME, van der Wal G, Ribbe MW. Pneumonia: the demented patient's best friend? Discomfort after starting or withholding antibiotic treatment. *J Am Geriatr Soc* 2002;50:1681-8.
68. Rozzini R, Sabatini T, Trabucchi M. Medical treatment of acute illnesses in end-stage dementia. *Arch Intern Med* 2003;163:496-7; author reply 7-8.
69. Morrison RS, Ahronheim JC, Morrison GR, et al. Pain and discomfort associated with common hospital procedures and experiences. *J Pain Symptom Manage* 1998;15:91-101.
70. Givens JL, Selby K, Goldfeld KS, Mitchell SL. Hospital transfers of nursing home residents with advanced dementia. *J Am Geriatr Soc* 2012;60:905-9.
71. Fried TR, Gillick MR, Lipsitz LA. Whether to transfer? Factors associated with hospitalization and outcome of elderly long-term care patients with pneumonia. *J Gen Intern Med* 1995;10:246-50.
72. Loeb M, Carusone SC, Goeree R, et al. Effect of a clinical pathway to reduce hospitalizations in nursing home residents with pneumonia: a randomized controlled trial. *JAMA* 2006;295:2503-10.
73. Kyne L, Merry C, O'Connell B, Kelly A, Keane C, O'Neill D. Factors associated with prolonged symptoms and severe disease due to *Clostridium difficile*. *Age Ageing* 1999;28:107-13.
74. van der Steen JT, Mehr DR, Kruse RL, et al. Predictors of mortality for lower respiratory infections in nursing home residents with dementia were validated transnationally. *J Clin Epidemiol* 2006;59:970-9.
75. Faulkner CM, Cox HL, Williamson JC. Unique aspects of antimicrobial use in older adults. *Clin Infect Dis* 2005;40:997-1004.
76. Givens JL, Kiely DK, Carey K, Mitchell SL. Healthcare proxies of nursing home residents with advanced dementia: decisions they confront and their satisfaction with decision-making. *J Am Geriatr Soc* 2009;57:1149-55.
77. Albrecht JS, McGregor JC, Fromme EK, Bearden DT, Furuno JP. A nationwide analysis of antibiotic use in hospice care in the final week of life. *J Pain Symptom Manage* 2013;46:483-90.
78. Furuno JP, Noble BN, Horne KN, et al. Frequency of outpatient antibiotic prescription on discharge to hospice care. *Antimicrob Agents Chemother* 2014;58:5473-7.
79. Rosenberg JH, Albrecht JS, Fromme EK, et al. Antimicrobial use for symptom management in patients receiving hospice and palliative care: a systematic review. *J Palliat Med* 2013;16:1568-74.
80. Thompson AJ, Silveira MJ, Vitale CA, Malani PN. Antimicrobial use at the end of life among hospitalized patients with advanced cancer. *Am J Hosp Palliat Care* 2012;29:599-603.
81. Hickman SE, Nelson CA, Perrin NA, Moss AH, Hammes BJ, Tolle SW. A comparison of methods to communicate treatment preferences in nursing facilities: traditional practices versus the physician orders for life-sustaining treatment program. *J Am Geriatr Soc* 2010;58:1241-8.

82. Loeb M, Brazil K, Lohfeld L, et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomised controlled trial. *Bmj* 2005;331:669.
83. Monette J, Miller MA, Monette M, et al. Effect of an educational intervention on optimizing antibiotic prescribing in long-term care facilities. *J Am Geriatr Soc* 2007;55:1231-5.
84. Naughton BJ, Mylotte JM, Ramadan F, Karuza J, Priore RL. Antibiotic use, hospital admissions, and mortality before and after implementing guidelines for nursing home-acquired pneumonia. *J Am Geriatr Soc* 2001;49:1020-4.
85. Hutt E, Ruscini JM, Corbett K, et al. A multifaceted intervention to implement guidelines improved treatment of nursing home-acquired pneumonia in a state veterans home. *J Am Geriatr Soc* 2006;54:1694-700.
86. Zimmerman S, Mitchell M, Beeber AS, et al. Strategies to Reduce Potentially Inappropriate Antibiotic Prescribing in Assisted Living and Nursing Homes. In: *Advances in the Prevention and Control of HAIs*. Rockville, MD: Agency for Healthcare Research and Quality 2014:99-109.
87. Zimmerman S, Sloane PD, Bertrand R, et al. Successfully reducing antibiotic prescribing in nursing homes. *J Am Geriatr Soc* 2014;62:907-12.
88. Juthani-Mehta M, Malani PN, Mitchell SL. Antimicrobials at the End-of-Life: An Opportunity to Improve Palliative Care and Infection Management. *Journal of the American Medical Association* 2015;In press.
89. Trautner BW, Grigoryan L, Petersen NJ, et al. Effectiveness of an Antimicrobial Stewardship Approach for Urinary Catheter-Associated Asymptomatic Bacteriuria. *JAMA Intern Med* 2015;175:1120-7.
90. Meeker D, Linder JA, Fox CR, et al. Effect of Behavioral Interventions on Inappropriate Antibiotic Prescribing Among Primary Care Practices: A Randomized Clinical Trial. *JAMA* 2016;315:562-70.
91. Anderson RA, Issel LM, McDaniel Jr RR. Nursing homes as complex adaptive systems: relationship between management practice and resident outcomes. *Nurs Res* 2003;52:12-21.
92. Rantz MJ, Flesner MK, Zwygart-Stauffacher M. Improving care in nursing homes using quality measures/indicators and complexity science. *J Nurs Care Qual* 2010;25:5-12.
93. Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q* 1966;44:Suppl:166-206.
94. Stewart AL, Teno J, Patrick DL, Lynn J. The concept of quality of life of dying persons in the context of health care. *J Pain Symptom Manage* 1999;17:93-108.
95. Donner A, Birkett N, Buck C. Randomization by cluster. Sample size requirements and analysis. *Am J Epidemiol* 1981;114:906-14.
96. Donner A, Klar N, eds. *Design and Analysis of Cluster Randomization Trials in Health Research*. London, U.K.: Arnold Publishing Co; 2000.
97. Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. *Implement Sci* 2012;7:50.
98. Mitchell SL, Miller SC, Teno JM, Kiely DK, Davis RB, Shaffer ML. Prediction of 6-month survival of nursing home residents with advanced dementia using ADEPT vs hospice eligibility guidelines. *JAMA* 2010;304:1929-35.
99. Kiely DK, Givens JL, Shaffer ML, Teno JM, Mitchell SL. Hospice use and outcomes in nursing home residents with advanced dementia. *J Am Geriatr Soc* 2010;58:2284-91.
100. Mitchell SL, Kiely DK, Jones RN, Prigerson H, Volicer L, Teno JM. Advanced dementia research in the nursing home: the CASCADE study. *Alzheimer Dis Assoc Disord* 2006;20:166-75.
101. Mitchell SL, Tetroe J, O'Connor AM. A decision aid for long-term tube feeding in cognitively impaired older persons. *J Am Geriatr Soc* 2001;49:313-6.
102. Hanson LC, Carey TS, Caprio AJ, et al. Improving decision making for feeding options in dementia care: a randomized trial. *J Am Geriatr Soc* 2011 In press.

103. Volandes AE, Paasche-Orlow MK, Barry MJ, et al. Video decision support tool for advance care planning in dementia: randomised controlled trial. *BMJ* 2009;338:b2159.
104. Catic AG, Berg AI, Moran JA, et al. Preliminary data from an advanced dementia consult service: integrating research, education, and clinical expertise. *J Am Geriatr Soc* 2013;61:2008-12.
105. Fisch J, Lansing B, Wang L, et al. New acquisition of antibiotic-resistant organisms in skilled nursing facilities. *J Clin Microbiol* 2012;50:1698-703.
106. Givens JL, Spinella S, Ankuda CK, et al. Healthcare Proxy Awareness of Suspected Infections in Nursing Home Residents with Advanced Dementia. *J Am Geriatr Soc* 2015;63:1084-90.
107. D'Agata EM, Habtemariam D, Mitchell S. Multidrug-Resistant Gram-Negative Bacteria: Inter- and Intradissemiation Among Nursing Homes of Residents With Advanced Dementia. *Infect Control Hosp Epidemiol* 2015;36:930-5.
108. Mitchell SL, Teno JM, Roy J, Kabumoto G, Mor V. Clinical and organizational factors associated with feeding tube use among nursing home residents with advanced cognitive impairment. *JAMA* 2003;290:73-80.
109. Engel SE, Kiely DK, Mitchell SL. Satisfaction with end-of-life care for nursing home residents with advanced dementia. *J Am Geriatr Soc* 2006;54:1567-72.
110. Recommendations of regulatory issues in cluster studies. US Department of Health and Human Services, 2014. (Accessed January 12, 2016, at <http://www.hhs.gov/ohrp/sachrp/commsec/attachmentjul32014:recommendationsonregulatoryissuesinclustersudies.html>.)
111. D'Agata EM, Magal P, Olivier D, Ruan S, Webb GF. Modeling antibiotic resistance in hospitals: The impact of minimizing treatment duration. *J Theor Biol* 2007.
112. Simone MJ, Roberts DH, Irish JT, et al. An educational intervention for providers to promote bone health in high-risk older patients. *J Am Geriatr Soc* 2011;59:291-6.
113. Volicer L, Hurley AC, Lathi DC, Kowall NW. Measurement of severity in advanced Alzheimer's disease. *J Gerontol* 1994;49:M223-6.
114. Gozalo P, Teno JM, Mitchell SL, et al. End-of-life transitions among nursing home residents with cognitive issues. *N Engl J Med* 2011;365:1212-21.
115. Mitchell SL, Teno JM, Intrator O, Feng Z, Mor V. Decisions to forgo hospitalization in advanced dementia: a nationwide study. *J Am Geriatr Soc* 2007;55:432-8.
116. Hilbe JMH. *Negative Binomial Regression*. Cambridge Cambridge University Press; 2007.
117. Cheng SC, Fine JP, Wei LJ. Prediction of cumulative incidence function under the proportional hazards model. *Biometrics* 1998;54:219-28.
118. Schafer JL. *Analysis of Incomplete Multivariate Data*. London: Chapman & Hall; 1997.
119. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. Second ed. New York: John Wiley & Sons; 2002.
120. Signorini D. Sample size for Poisson regression. *Biometrika* 1991;78:446-50.

## 20 SUPPLEMENTS/APPENDICES