Trial to Reduce Antimicrobial Use In Nursing home residents with Alzheimer's disease and other Dementias (TRAIN-AD)
Statistical Analysis Plan for the Final Report

PROTOCOL NUMBER: IRB-2016-23

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

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FUNDING AGENCIES: National Institutes of Health (R01AG032982)

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Version Number	Revision(s) and Reason(s) for Amendment	Release Date
1.0		24 June 2017
2.0	*Aims 1 and 2:* *Additional detail has been added to the analysis plan to clarify that all residents contribute to these analyses regardless of whether or not the resident has experienced a suspected LRI or UTI.* *Aim 3:* *1) The outcome of documented discussion between providers and proxies about infection management has been removed since these data are not collected.* *2) For advance directives regarding use of antimicrobials, we have clarified that this analysis subsets to remove those residents who began the study with advance directives restricting **all** routes of antimicrobial use. Acquiring an advance directive regarding antimicrobial use could arise by a) having no directives and acquiring any new directive, or b) having a less restrictive directive and acquiring a new more restrictive directive.* *3) In addition to examining the combined outcome of burdensome interventions, each type of burdensome intervention will be examined separately.*	30 June 2018
3.0	*Aim 3:* *The exploratory analysis section for Aims H3a and H3b has been updated to indicate adjustment for competing risks will only be undertaken for Aim H3a, since Aim H3b does not include a time-to-event analysis.*	15 September 2018
4.0	*1) In Section 3.5, additional detail has been added to clarify the primary analysis.* *2) Sensitivity analyses or exploratory analyses previously described in Section 3.5 have been moved to Section 3.6 for consistency.*	15 February 2019
5.0	*In Section3.6, an additional exploratory analysis has been added to compare antimicrobial courses prescribed for any reason.*	15 April 2019
6.0	*In Sections 1.1, 1.2, 1.5, 1.8, and 3.5, the sample size has been revised to reflect the decision to increase the number of nursing homes to 28 to account for lower than expected average enrollment per nursing home.*	30 June 2019

7.0	*In Section 3.5, the primary analysis has been updated to reflect it will include adjustment for the two variables we sought to balance with constrained randomization, for-profit status of the nursing home and resident race.*	15 April 2020

PREFACE

The Statistical Analysis Plan (SAP) as outlined in this document will be finalized prior to the completion of the study and analysis of final study data. The SAP contains all modifications and updates to the planned analyses that were outlined in the original study protocol. This plan details all a priori specified analyses that will be performed upon study completion and database lock, with specifications for tables, figures, and statistical models. Tables and figures that are to be included in interim reporting are indicted with an (*) for overall or (**) for by intervention group (partially blinded) after the title.

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Analysis plan Version 1.0 approved by:

	June 23, 2017
Susan L. Mitchell, MD, MPH Principal Investigator	Date

	23 June 2017
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_____ _____

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Susan L. Mitchell, MD, MPH — Date
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6 April 2020

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1 Overview

1.1 Study Rationale and Design

The final stage of dementia is characterized by recurrent suspected infections. Research has shown these episodes are widely mismanaged, leading to adverse patient and public health outcomes. Antimicrobials are extensively prescribed in advanced dementia, most often in the absence of clinical evidence to support a bacterial infection. Antimicrobial exposure is the main risk factor for multidrug-resistant organisms (MDROs). Nursing home (NH) residents with advanced dementia are three times more likely to be colonized with MDROs compared to other residents. Moreover, as these patients are in the terminal phase of dementia, evidence suggests they may not clinically benefit from antimicrobials. Comfort is the stated goal of care for 90% of advanced dementia patients, and the risks and burdens associated with work-up and treatment of suspected infections generally do not promote that goal, particularly when hospitalization is involved. Taken together, there is a clear need to improve infection management in advanced dementia both to provide better end-of-life care to these patients and reduce the public health threat of MDROs.

This is a 52-month study (8 months preparation; 36 months to conduct the trial; 8 months data analyses and manuscript preparation) of a cluster randomized controlled trial (RCT) of an intervention to improve infection management for suspected UTIs and LRIs among residents with advanced dementia (N=410; N=205/arm) living in NHs (N=28; N=14/arm). The NH is the unit of randomization as the intervention must be delivered at the facility level to avoid contamination and because this is how it would be employed in the real-world. Analyses will be at the patient level.

1.2 Objectives and Outcomes

The Specific Aims are:

Aim 1. To conduct a cluster RCT of an intervention to improve infection management among 410 residents with advanced dementia (N=205/arm) residing in 28 NHs (N=14/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.

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 (secondary outcome) 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 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.

1.3 Inclusion and Exclusion Criteria

Inclusion criteria:

A. Residents

The eligibility criteria and protocol to identify NH residents with advanced dementia will be similar to those used in the 4 prior R01s and the pilot R21 preceding this trial, which together have identified >2300 such residents. Resident eligibility criteria are: 1) age > or = to 60 years, 2) A diagnosis of dementia (any type), 3) Global Deterioration Scale (GDS) score of 7, 4) NH length of stay >90 days, and 5) an individual who can communicate in English has been formally or informally designated as a health care proxy (95% family members in prior studies). GDS stage 7 features include: profound memory deficits (cannot recognize family), total functional dependence, speech <= 5 words, incontinence, and non-ambulatory.

GDS 7 was chosen to define advanced dementia as it has been successfully operationalized and validated in our 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.

At baseline and q2months for 1 year, a research assistant will interview nurses on each NH unit to identify eligible residents. Eligibility will be confirmed by chart review.

B. NH Providers in Intervention Nursing Homes

Eligibility criteria for providers in the intervention nursing homes include: a nurse, nurse practitioner, physician or physician assistant identified by a senior administrator as an individual who cares for residents with advanced dementia, able to communicate in English (because intervention materials are all in English), and over 21 years of age.

In partnership with the nursing homes leadership, the TRAIN-AD intervention will be rolled out as a new program within the facility. Within that context, the provider educational component of TRAIN-AD intervention will target the “usual” providers in that nursing home who commonly care for advanced dementia residents, i.e., dedicated employees (e.g.,

nurses) and medical providers with privileges (e.g., physicians, nurse practitioners, physician assistants).

Exclusion criteria:

Residents with cognitive impairment due to causes other than dementia (e.g., head trauma and in short-term, sub-acute SNFs) will be excluded.

Residents' whose proxies cannot communicate in English will be excluded from the study, because the information directed to proxies are only in English.

Providers that do not provide direct care to residents with advanced dementia or who do not speak English.

1.4 Duration of Participation and Duration of Study

This is a 52-month study (8 months preparation, 36 months to conduct the trial and 8 months of data analyses and manuscript preparation. At each participating facility there will be a 3 month start-up period, 12-months resident screening and enrollment and up to 24 months data collection total (12 months follow-up for each resident deemed eligible over the 12 months screening).

1.5 Facility Randomization procedures

The study will be conducted in 28 NHs (14/arm). NHs will be brought on in 6 waves. Six NHs will be enrolled per wave for the first four waves; 3 NHs randomized to the control group and 3 NHs randomized to the intervention group. The last two waves will enroll two nursing homes (1 control/1 intervention) per wave. The size of waves will be increased if needed to replace NHs that drop out prior to enrollment. The 6 waves will begin three months apart such that by 18 months all 24 facilities will be on board. One month prior to the start of each wave, the project director (PD) will send the list of the facilities recruited to that wave to the statistician using a confidential study identification number. Only the project PD will know the name of the facility associated with its identification number. Once the statistician completes randomization, she will email the facility assignments back to the PD.

Randomization of NHs will be based on a modified minimization algorithm, where the NH factors to be balanced will be: for profit status, estimated number of severely cognitive impaired residents (Clinical Frailty Scale (CFS)=3), and estimated number of African American residents. These NH characteristics will be ascertained from the Brown LTCFocus website using data from 2015. The number of high CFS residents and African American residents will be operationalized as binary variables divided at the median. For the first wave of 6 NHs, all possible ways of assigning 3 NHs to each group will be considered, and we will select the assignment that minimizes the imbalance across the three factors. If more than one assignment has the best imbalance score, one of these assignments will be chosen randomly. For the second wave, all assignments of 3 nursing homes to each group will be considered as well as the imbalance score of the original wave to yield the best overall balance. Similarly, waves three and four will consider all assignments of three NHs to each group, and waves 5 and 6 all assignments of one

NH to each group, and take into account the imbalance scores accumulating from previous waves to yield the best overall balance.

1.6 Interim Data Safety Reviews

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 Missiouri. The PI will meet with Dr. Mehr duration 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 adverse events 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, and protocol deviations, and outcomes (only 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.

1.7 Interim Analyses and Stopping Rules

The DSM will be free to determine the need to stop the continuation of the study based on examination of data safety and monitoring reports; however, there are no interim analyses or *a priori* stopping rules established for this minimal risk study.

1.8 Rationale for Number of Residents

Calculations use two-sided testing, assuming a type I error rate of 5% and 90% power, and adjust for potential dependence of observations within NHs using an intracluster correlation of 0.01 based on data from the Study of Pathogen Resistance and Exposure to Antibiotics in Dementia (SPREAD) study conducted in 35 NHs. Based on SPREAD data, we estimate the total antimicrobial courses/person-year in the control arm will be ~1.26, of which 72% (0.91 courses/person-year) will not meet minimal criteria for treatment. Based on prior work, we estimate that we can reduce the % of courses not meeting minimal criteria in the intervention arm by 35%, for a reduction in total courses of 25% (0.72 X 0.35=0.25). We anticipate another 5% reduction in total courses by decisions to withhold antimicrobials in the intervention arm, for total reduction of 30% (25% + 5% = 30%), resulting in an absolute reduction of 0.38 (0.30 X 1.26=0.38) in total courses/person years in the intervention vs. control arms.

Sample size estimates were computed using an approach for comparing rates based on a simplified assumption of a Poisson distribution for the number of antimicrobial courses. To achieve at least 90% power in testing for an absolute reduction in antimicrobial courses/person year of 0.38, we require a total of 28 NHs (14 NHs/arm), assuming each NH contributes, on average, 15 residents (total 410 residents; 205/arm) and each resident contributes, on average, 0.79 person-years based on SPREAD data. With this sample size, repeated power calculations for H1 using a more complex simulation of the negative binomial-logit hurdle model found that we will have > 90% for testing the joint effect of the intervention reducing the probability of having at least one antimicrobial course, and given any antimicrobial use, the number of courses. The sample size also provides adequate power to detect meaningful effect sizes for Aims 2 and 3. Control rates are based on prior studies; ~13% of residents will have advance care planning for infection management (documented provider-proxy discussions or new

directives to withhold antimicrobials) and experience 3.25 burdensome procedures/person-year for UTIs and LRIs.

2 Reporting

2.1 Data Flow

Dr. Mitchell will oversee the training of the field staff for two months prior to starting data collection. One research Assistant (RA) will be responsible for screening subjects and conducting chart reviews. To the extent possible, the RA collecting outcome data through chart reviews will be blinded to nursing home randomization. All data will be collected and entered electronically by the RA using laptop computers in the field. Electronic data capture software and programming (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. 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. All staff involved in the study will receive training in the protection of human subjects.

Data management and analysis for the study will take place at Hebrew SeniorLife (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. In order to preserve confidentiality, subjects will be assigned a study number known only to the co-PIs, RAs and data manager. All physical documentation and IT assets are stored in a locked area at 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.

2.2 Report Generation

The final statistical report will describe and justify any deviations from the original statistical plan described herein. If necessary, such deviations will be treated as a protocol amendment.

The final statistical report will be accompanied by a description of the data cleaning process and will provide summaries of key findings. All programs used to produce the statistical reports will be documented, tested, and archived.

2.3 Definitions of Analysis Populations

Intent-to-Treat (ITT) Population:

All eligible residents enrolled into the study will be included in the ITT population. The ITT population will be the primary analysis population for all primary and secondary outcomes.

Safety Population:
As randomization is at the level of NH, the safety population will be coincidental with the ITT population for this study.

3 Overview of Planned Analyses

3.1 Recruitment and Participant Status

Total residents over time will be summarized overall and by intervention group. The number of residents screened, enrolled, withdrawn, and completing the study will be summarized overall and by intervention group. Reasons for screen failure and dropout will be summarized overall and by intervention group.

The corresponding descriptive summaries are outlined in Appendix A, Section A.1.

3.2 Resident Demographics and Baseline Characteristics

Demographic and clinical characteristics of residents at baseline will be summarized by intervention arm. Resident characteristics will include measures of demographic information, health status, cognitive status, functional status, and advance care planning.

The corresponding descriptive summaries are outlined in Appendix A, Section A.2.

3.3 Adverse Events

The study has been granted minimal risk status by the NIH. Patients with advanced dementia are very frail. In the natural course of the disease, we expect a 40% mortality rate over one year. Thus, deaths 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 the treatments as defined by our primary outcome.

The are no anticipated serious adverse events or adverse events in this study. Any unanticipated adverse events will be compared between intervention groups using chi-square tests or Fisher's exact tests as appropriate. The corresponding descriptive summaries are outlined in Appendix A, Section A.3.

3.4 Protocol Deviations and Unanticipated Problems

Any protocol deviations or unanticipated problems will be listed by intervention group and summary statistics such as frequencies and percentages will be included if appropriate. The corresponding listings and descriptive summaries are outlined in Appendix A, Section A.4.

3.5 Primary and Secondary Outcomes

The analytic plan will examine the effect of the intervention by comparing data collected from 410 NH residents with advanced dementia (N=205/arm) in 28 NHs (14/arm) in the intervention vs. control arms. The primary outcome is the number or antimicrobial courses for suspected UTIs and LRIs/person-year over 12 months (Aim 1). Secondary outcomes are: antimicrobial courses for suspected UTIs and LRIs when minimal criteria for initiation are absent/person-year (Aim 2); advance care planning for infection management (Aim 3, H3a), and burdensome procedures/person-days to evaluate suspected LRIs and UTIs (Aim 3, H3b).

Descriptive analyses will include frequencies for categorical variables and means/medians with SDs/interquartile ranges for continuous variables. Outcomes will be compared between arms using negative binomial-logit hurdle regression models (H1, H2, and H3b) and Cox proportional hazards regression (H3a), with robust estimates of variance to account for clustering within NHs. All analyses will be at the resident level and follow intention to treat principles. The primary analysis will include intervention and the two variables we sought to balance with constrained randomization, for-profit status of the NH and resident race. Sensitivity analyses will adjust for imbalances in resident features, as needed. While we do not anticipate an effect on mortality, analyses will account for the competing risk of death and differential follow-up time due to mortality. Analyses will be done with SAS (SAS Institute, Inc., Cary, NC), Stata (College Station, TX), and R (R Foundation for Statistical Computing, Vienna).

Aim 1: Compare antimicrobial courses for suspected UTIs and LRIs/person-years (primary outcome).

For H1, the number of antimicrobial courses for suspected UTIs and LRIs/person-years over 12 months will be compared between the study arms using negative binomial-logit hurdle regression models. This approach accommodates a potential excess of residents not receiving antimicrobials by using a two-stage process: a logit model examining the probability of receiving a least one antimicrobial course, and among those receiving at least one course, a truncated negative binomial model examining the number of courses. Length of follow-up (time to death, dropout, or study completion) will be included as an offset. Analyses will be at the resident-level. All residents contribute data for this analysis. A resident who experiences one or more suspected infections will have their number of antimicrobial courses associated with these episodes summed as the outcome, with the length of follow-up as the offset. A resident who experiences **no** suspected infections, will have 0 antimicrobial courses as the outcome, with the length of follow-up as the offset. Robust estimates of variance will account for clustering within

NHs. The logit portion of the model will generate ORs and the negative binomial portion will generate rate ratios (RRs), both with 95% CIs. A two-sided likelihood ratio test will jointly test whether the intervention reduces the probability of having at least one antimicrobial course, and given any antimicrobial use, the number of courses.

Aim 2: Compare total antimicrobial courses for suspected UTIs and LRIs when minimal criteria for initiation are absent/person-years (secondary outcome).

For H2, total antimicrobial courses for suspected UTIs and LRIs when minimal criteria for initiation are absent/person-years over 12 months will be compared between the intervention and control arms. As in our prior studies, the determination that a treated episode did not meet minimal criteria will be based on consensus guidelines using signs and symptoms documented in the residents' charts. The analytic approach to H2 will be the same as that described for H1. All residents contribute data for this analysis. A resident who experiences one or more suspected infections when minimal criteria for initiation were absent will have their number of antimicrobial courses associated with these episodes summed as the outcome, with the length of follow-up as the offset. A resident who experiences **no** suspected infections when minimal criteria for initiation were absent, will have 0 antimicrobial courses as the outcome, with the length of follow-up as the offset.

Aim 3: Compare: i. advance care planning and ii. use of burdensome procedures (secondary outcomes).

For H3a, the analysis will compare advance care planning for infections over 12 months defined as having no advance directives to withhold antimicrobials and acquiring a new advance directive to withhold antimicrobials by any route (oral, intramuscular, or intravenous) or having a less restrictive directive to withhold antimicrobials and acquiring a more restrictive directive to withhold antimicrobials. Residents with directives restricting all routes of antimicrobial use at baseline will be excluded. Time to the date of the new directive will be compared between arms using Cox proportional hazards regression modeling with a robust variance estimate to account for clustering at the NH level. Residents who die, dropout, or complete the study without these directives will be censored. HRs and 95% CIs will be generated. For H3b, the main analysis will compare the total number of burdensome procedures (bladder catheterizations, blood draws, chest x-rays, and hospital transfers) used to evaluate a suspected UTI or LRI/person-years between arms. The analytic approach will be same as described for H1.

3.6 Approach to Missing Data, Sensitivity Analyses and Exploratory Analyses

All analyses will follow the intention to treat principle. Based on prior studies, we estimate that 40% of residents will die over 12 months and <1% will be lost to follow-up for other reasons. Residents will contribute data to the analyses up until death (post-death chart review). We will compare the characteristics of residents with missing data to those with complete data. As needed, sensitivity analyses will be performed and imputation techniques employed to account for missing data. The effect of imbalances between key resident characteristics on the intervention effect will be examined as sensitivity analyses using the change-in-effect method.

For H1, an exploratory analysis will examine antimicrobial courses prescribed for any reason (i.e., not limited to antimicrobials prescribed for suspected UTIs or LRIs). We will compare the number of antimicrobial courses/person-years between the intervention and control arms.

For H1 and H2, exploratory analyses will examine UTIs and LRIs separately.

For H3a, a sensitivity analysis will be conducted to examine if the potential competing risk of death impacts the estimates of cumulative incidence using the Fine-Gray regression model.

For H3b, in addition to examining the combination of all burdensome procedures, each type of burdensome procedure (bladder catheterizations, blood draws, chest x-rays, and hospital transfers) will be examined separately, using a similar analytic approach, as exploratory analyses.

Appendix A: Tables and Figures

Specifications for planned tables and figures are provided below. Cosmetic changes in style and formatting may be made as needed for presentation and publication requirements.

A.1 Recruitment and Participant Status

Table A.1.1. Overall Overview of Resident Enrollment over Time*

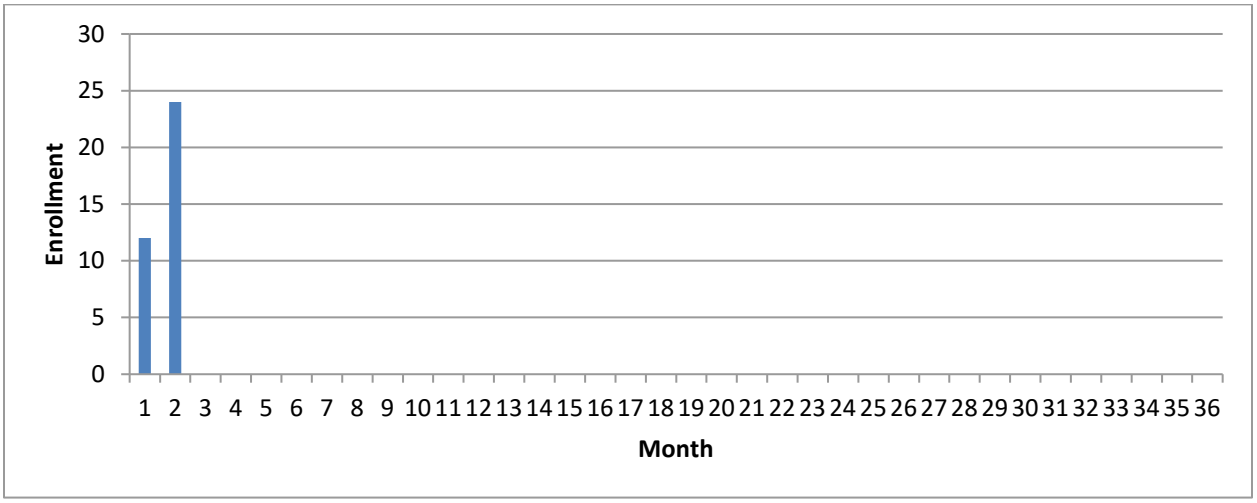
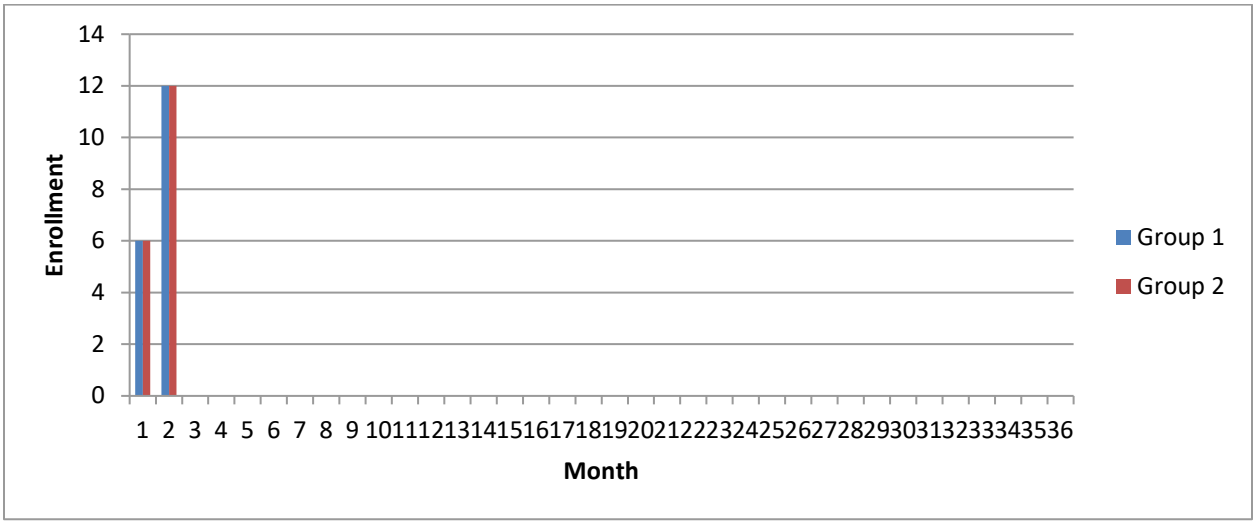


Table A.1.2. Event Completion for All Participants*

Study Event	Residents
Baseline	
Q1	
Q2	
Q3	
Q4	
Death	

Table A.1.3. Overview of Resident Enrollment over Time by Group**



A.2 Resident Demographics and Baseline Characteristics

Table A.2.1. Demographics and Baseline Characteristics of Residents Overall and by Group

	Total in Study	Group 1	Group 2	Non-Participants
Resident				
Age				
Mean (Median)				
Gender				
Male				
Female				
Race				NA
Black				
White				
Other				
Ethnicity				NA
Hispanic				
Non-Hispanic				
Other				
Health status				NA
Cognitive status				NA
Functional status				NA
Advance care planning				NA

A.3 Adverse Events

Table A.3.1. Overall Listing and Summary of Adverse Events*

Date	Description of Adverse Event	Action Taken	*Outcome*
Total # of Adverse events			

Table A.3.2. Listing and Summary of Adverse Events by Group**

Number	Date	Description of Adverse Event	*Action Taken*	*Group*
1				
2				
3				
4				
5				
6				
Total # of Adverse events				
Total Withdrawn from study				

A.4 Protocol Deviations and Unanticipated Problems

Table A.4.1. Overall Listing and Summary of Protocol Deviations*

Number	Date	Protocol Deviation
1		
2		
3		
4		
5		
6		
Total # of Deviations		
Participants Enrolled		
Deviations per Participant		

Table A.4.2. Listing and Summary of Protocol Deviations by Group**

Number	Date	Protocol Deviation	Group
1			
2			
3			
4			
5			
6			
Total # of Deviations			

Number	Date	Protocol Deviation	Group
Participants Enrolled			
Deviations per Participant			

Table A.4.3. Overall Listing and Summary of Unanticipated Problems*

Number	Date	Unanticipated Problem
1		
2		
3		
4		
5		
6		
Total # of Problems		
Participants Enrolled		
Problems per Participant		

Table A.4.4. Listing and Summary of Unanticipated Problems by Group**

Number	Date	Unanticipated Problem	Group
1			
2			
3			
4			
5			
6			
Total # of Problems			
Participants Enrolled			

Number	Date	Unanticipated Problem	Group
Problems per Participant			