APPROACHES: ALIGNING PATIENT PREFERENCES – A ROLE OFFERING ALZHEIMER'S PATIENTS, CAREGIVERS, AND HEALTHCARE PROVIDERS EDUCATION AND SUPPORT

A Nursing Home Pragmatic Clinical Trial

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PRÉCIS

Study Title

APPROACHES: Aligning Patient Preferences – a Role Offering Alzheimer's patients, Caregivers, and Healthcare providers Education and Support

Objectives

APPROACHES is a pragmatic cluster randomized control trial testing the impact of a structured ACP specialist program on patients with Alzheimer's and dementia related diseases in nursing homes.

1.1 Primary Objective R33 Phase (42 months)

1.1.1 Aim 1: Compare hospital transfers (admissions and emergency department visits) over 12 months between ADRD patients in intervention vs. control nursing homes

1.2.1.1 H1: Transfers will be lower among ADRD patients in intervention vs. control nursing homes.

1.2 Secondary Objective

1.2.1 Aim 2: Compare the following secondary outcomes between ADRD patients in intervention vs. control nursing homes over 12 months: 1) hospice enrollment; and 2) death in hospital.

1.2.2.1 H1: ADRD patients in the intervention vs. control nursing homes will have:

1.2.2.1.1 i. Greater hospice enrollment;

1.2.2.1.2 and ii. Lower rates of dying in the hospital.

Design and Outcomes

In intervention nursing homes, a nursing home provider (e.g. social worker or chaplain) will be trained as an ACP Specialist who will work with nursing home leaders to: i. Consolidate nursing home ACP procedures; ii. Train and educate staff; and iii. Facilitate ACP with patients and their family caregivers. Control nursing homes will apply the usual ACP practices. The implementation period will be 18 months. All ADRD patients in the nursing homes during the implementation will be followed for 12 months.

Sample Size and Population

A total of 142 nursing homes will be randomized to either an intervention or control arm within each corporation (Signature, N= 109; Miller's, N= 33).

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1 STUDY OBJECTIVES

1.1 Primary Objectives

1.1.1 Aim 1: Compare hospital transfers (admissions and emergency department visits) over 12 months between ADRD patients in intervention vs. control nursing homes.

1.2.1.1 H1: Transfers will be lower among ADRD patients in intervention vs. control nursing homes.

1.2 Secondary Objective

1.2.1 Aim 2: Compare the following secondary outcomes between ADRD patients in intervention vs. control nursing homes over 12 months: 1) hospice enrollment and 2) death in hospital.

1.2.2.1 H1: ADRD patients in the intervention vs. control nursing homes will have:

1.2.2.1.1 i. Greater hospice enrollment;

1.2.2.1.2 and ii. Lower rates of dying in the hospital.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

A significant number of patients Alzheimer's disease or related dementia diagnoses will be cared for in nursing homes near the end of life. Unfortunately, many of these patients experience unwanted and burdensome medical treatments, such as potentially avoidable hospitalizations, that negatively impact quality of life. Advance care planning (ACP) discussions with patients and family caregivers are important to explore goals in advance of a crisis and support informed, values-based decision-making. The ACP process helps to ensure that preferences about treatments such as hospitalization are known, documented, and honored. Research indicates that ACP can reduce burdensome treatments and increase the likelihood that care will match documented preferences. Nursing homes are currently required by regulations to offer ACP to patients and families. However, there are no training requirements for nursing home staff and approaches to fulfilling this regulatory and ethical responsibility vary widely, resulting in inconsistent ACP. The "Aligning Patient Preferences – a Role Offering Alzheimer's patients, Caregivers, and Healthcare providers Education and Support (APPROACHES)" trial will test the ACP Specialist Program. Existing nursing home staff members will be trained to enhance care and reduce unwanted, burdensome hospitalizations through improved ACP procedures, standardized staff education on ACP, and systematic ACP facilitation.

2.2 Study Rationale

The ACP Specialist Training courses will serve as an educational tool to provide training to the ACP Specialists at enrolled nursing facilities that engage in ACP conversations. This tool will help refine and improve their knowledge of how to best have and record these conversations by providing tips, examples, and information on nursing homes.

A majority (72%) of nursing home patients have cognitive impairment[1] and about half have a documented diagnosis of Alzheimer's Disease or a related dementia (ADRD).[2] As a result of the progressive, downward trajectory of ADRD,[3] 70% of patients live their final days in nursing homes.[4] These patients often receive burdensome and expensive

treatments that may be avoidable and even unwanted.[5,6] Hospitalizations are increasingly identified as a concern because of high burdens, high costs, and low clinical benefits in patients with advanced stages of dementia.[7] Advance care planning (ACP) provides family caregivers of ADRD patients with education and support in identifying and documenting goals of care to align treatments with preferences.[8] Documentation reflecting preferences for less aggressive treatment is associated with lower rates of hospitalization.[9,10,11] However, nursing home staff are rarely trained to facilitate ACP or provided with strategies to integrate into practice resulting in highly variable practice and inaccurate documentation.[6,7,12-18]

Under the auspices of a Centers for Medicare and Medicaid Services Initiative, our team has developed and successfully implemented a multi-component intervention to reduce avoidable hospitalizations of long-stay patients in 19 nursing homes across Indiana.[19,20] While the scalability and sustainability of the full intervention model remains untested, our experience to date indicates the ACP component is particularly practical, effective, and translatable. The proposed ACP Specialist Program will build on this foundation by refining the ACP component to target ADRD patients and their family caregivers. This intervention will be delivered by existing nursing home staff (e.g., social worker).

The over-riding objective of this proposal is to conduct a pragmatic cluster randomized controlled trial (RCT) of "Aligning Patient Preferences – a Role Offering Alzheimer's patients, Caregivers, and Healthcare providers Education and Support (APPROACHES)" that aims to improve ACP and goal-directed outcomes in nursing home patients with ADRD. In the R33 phase, we will conduct the full pragmatic RCT in partnership with 2 nursing home corporations (Signature HealthCARE and Miller's Health Systems) in a combined total of 142 diverse facilities in 8 states. Consistent with the spirit of a pragmatic trial, we will use existing data sources including electronic health records (EHR), the Minimum Data Set 3.0 (MDS), and Medicare Claims data to characterize the cohort and measure outcomes. Hospital transfers over 12 months among ADRD patients is the 1^{o} trial outcome.

3 STUDY DESIGN

A total of 142 nursing homes will be randomized to either an intervention or control arm within each corporation (Signature, N= 109; Miller's, N= 33). In intervention nursing homes, a nursing home provider (e.g. social worker) will be trained as an ACP Specialist who will work with nursing home leaders to: i. Consolidate nursing home ACP procedures; ii. Train and educate staff; and iii. Facilitate ACP with patients and their family caregivers. Control nursing homes will apply the usual ACP practices. The implementation period is expected to be 18 months. All ADRD patients in the nursing homes during the implementation will be followed for 12 months.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Facilities will be randomized to either the control arm or the intervention arm. This selection will take into account the choice of each organization considering half the organizations facilities are included in each arm.

The focus of the ACP Specialist will be patients with ADRD who reside in the nursing homes during the initiative, though other patients residing in the nursing home may benefit from it in keeping with the spirit of a pragmatic trial.[21] Only patients with ADRD will be included in the analysis. ADRD is defined to include cognitive impairment[1] or a documented diagnosis of dementia in the MDS. Patients will be excluded if they are currently enrolled in hospice at the start of the intervention period.

Eligible facilities who agree to participate in the trial will be stratified at two levels: corporate ownership (Signature HealthCARE and Miller's Health Systems) & average number of hospital transfers per 1000 person-days alive using 2017 MDS data provided by CMS. Facilities will be grouped into low versus high hospitalization rates, using the median rate for the nursing home system as the threshold value for dichotomization. Facilities will be randomized to the intervention or control within each strata at a 1-to-1 ratio. Specifically, randomization will occur at the facility level, meaning that all patients with ADRD in the intervention buildings are eligible for inclusion in the trial. Following random assignment, we will use all available facility and patient-level data to test the balance of the intervention and control arms.

Nursing home characteristics will be obtained from nursing home corporate partners and the MDS. Potentially eligible nursing homes will be reviewed by the Data Management and Analysis Workgroup in preparation for potential inclusion in the pragmatic cluster RCT. Problematic or unstable facilities will be removed in consultation with nursing home corporate leaders prior to randomization.

4.1 Inclusion Criteria

- Medicare-certified
- All residents with Alzheimer's disease and related dementias.
- > 50 licensed beds
- >50% of residents are long-stay (>100 days in the facility)

4.2 Exclusion Criteria

- Patients currently enrolled in hospice at the start of the intervention period
- Problematic or unstable nursing homes
- Defined by corporate leadership prior to randomization

4.3 Study Enrollment Procedures

- Enrollment is occurring at the facility level; individual patients are not being enrolled.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Following randomization, the ACP Specialist program will be rolled out to the intervention buildings. All communications will be tailored to fit the corporate branding style of Signature HealthCARE and Miller's Health Systems. Communications about the ACP Specialist Program with individual facilities will be delivered by the Corporate Implementation Champion and the designated ACP Specialists, with, at minimum, monthly meetings with the project team to discuss issues and any unmet needs. At the conclusion of the pragmatic cluster RCT, we will merge our data and analyze to measure

our primary and secondary outcomes.

6 STUDY PROCEDURES

6.1 Description of Evaluations

6.1.1. Enrollment, Baseline, and/or Randomization

Nursing home Eligibility: All Medicare-certified nursing homes are eligible at Signature HealthCARE and Miller's Health Systems.

Nursing home Recruitment & Characteristics:
The ACP Specialist Program will be rolled out as a corporate initiative and nursing home Executive Directors will be requested to participate in the initiative by nursing home corporate leadership. It is anticipated all nursing home Executive Directors who are approached will agree to participate.

Nursing home corporate partners each provided data about key nursing home characteristics. At the time of randomization Signature HealthCARE owns 109 nursing homes in 8 states, with a total of 8,811 beds; 43% are rural. Miller's Health Systems owns 33 nursing homes, all in Indiana with 3,066 beds; 55% are rural. The mix of rural and urban facilities will provide a rich environment for this pragmatic trial. Self-reported 30-day hospital readmission rates for 2016 range from 13% for Miller's Health Systems and 17% for Signature HealthCARE nursing homes.

Random Assignment: Nursing homes will be sorted into groups that are comparable on hospital transfer rates. Eligible facilities who agree to participate in the trial will be stratified at two levels: corporate ownership (Signature HealthCARE and Miller's Health Systems) & average number of hospital transfers per 1000 person-days alive using 2017 MDS data. Facilities will be grouped into low versus high hospitalization rates, using the median rate for the nursing home system as the threshold value for dichotomization. Facilities will be randomized to the intervention or control within each strata at a 1-to-1 ratio. Specifically, randomization will occur at the facility level, meaning that all patients not currently on hospice at the start of the intervention period in the intervention buildings are eligible for inclusion in the trial. The intervention focuses on patients with ADRD, but other residents of intervention facilities are not excluded. Following random assignment, we will use all available facility and patient-level data to test the balance of the intervention and control arms.

7 SAFETY ASSESSMENTS

IRB has determined this study to be minimal risk.

Although this study includes a vulnerable population of patients with cognitive impairment, it is anticipated that this study will be determined to represent no more than minimal risk to patients and family caregivers. All nursing homes are required to offer ACP to patients and family caregivers as part of routine care. This requirement is inclusive of patients with cognitive impairment or ADRD. Therefore, the ACP Specialist Program is consistent with the standard of care and the risk of harm is no greater than those ordinarily encountered in the daily life of a nursing home patient or family caregiver who may be offered the opportunity to engage in ACP by nursing home staff.

According to 45 CFR 46.102 (OHRP 2017),[22] research is considered to pose minimal risk if the likelihood and degree of harm or discomfort anticipated from the research is no greater than that ordinarily encountered during daily life.

7.1 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

The potential serious negative reaction (SNR) that could occur during this trial is serious patient or family caregiver distress when engaging in ACP with the ACP Specialist. Based on our experience and results from other research studies, we anticipate that this will be rare. Serious distress could be demonstrated by negative reactions such as anger, uncontrolled crying, or early termination of an ACP discussion with the Specialist. The nature of these discussions is sensitive and personal, thus expressions of emotion, including tears, is expected and would not be considered a SNR. Training of the ACP Specialist will include emphasis on the importance of asking permission to begin an ACP conversation and respecting patient and family refusals. It will also include provision of emotional support and empathic statements during discussions. ACP Specialist training will include recognition of SNRs and instruction. In the R33 phase, staff will be instructed to report any negative reactions immediately to the Executive Director and the nursing home Corporate Implementation Champion. Together, these health care providers will evaluate the severity of the event and, if deemed serious, will report the SNR to the research team project manager via email or fax within 24 hours of the event. The project manager will report the SNR to both co-PIs via email or telephone immediately upon becoming aware of the event and will also notify the TBN Data and Safety Monitoring Board (DSMB) Chair in writing (email and hard copy) within 48 hours. The Co-PIs will take ultimate responsibility for ensuring the DSMB chair is informed in a timely manner. Follow-up includes checking in with the patient or family caregiver within 6 to 24 hours of the initial SNR to assess whether further intervention is needed to mitigate the SNR. If necessary, the patient or family caregiver should be referred for follow-up (e.g., referring family caregiver to primary care provider or community mental health facility).

We do not believe any potential consequences of APPROACHES would be considered serious adverse events (SAEs). We do not believe that death should be considered an SAE for this trial as: 1) death is often not unexpected in this nursing home population with ADRD; 2) death is not an adverse outcome for patients and families with goals of comfort or palliation if those goals are met; and 3) it is not known whether or not

aggressive care provided at the hospital results in lower mortality compared with conservative care in the nursing home.

In this pragmatic trial, we will work closely with the nursing home corporate partners deploying the intervention in order to monitor the overall safety of patients in the project, minimize any risk associated with the research, and protect confidentiality. After the initiation of the R33, the nursing home Corporate Implementation Champions and nursing home Corporate Data Experts from each of the 2 nursing home partners will participate in monthly meetings to discuss project implementation and address questions, problems, or concerns that might arise, including data safety and risk to patients.

Co-PIs Hickman and Unroe will continue to actively monitor for any results of other new research studies or regulatory policies that may have an impact on APPROACHES. Further, we will request the DSMB members to monitor for any external scientific or therapeutic developments that could impact the ethics of the trial or safety of participants

7.2 Safety Monitoring

The Co-PI Hickman will be responsible for executing the DSMP in her role as the lead for the Regulatory and Operations Workgroup. Co-PI Unroe, the project manager, data manager, information technology (IT) support person, and the IT representatives for each of the two partner institutions will all participate in the Regulatory and Operations Workgroup. This workgroup will also be responsible for obtaining appropriate agreements for nursing home health system partners, including Memoranda of Understanding (MOU) and Data Use Agreements (DUA) prior to any data transfer. This workgroup has oversight of submission of CMS data requests, that must include all data security precautions, as well as submission of the protocol to the Indiana University Indianapolis (IUI) Institutional Review Board (IRB) for review and approval. The Regulatory and Operations workgroup will also support the coordination of DSMB. All study personnel, including PIs, Co-Is, consultant, project manager, and nursing home Corporate Implementation Champions will complete online education in the Protection of Human Research Practice and complete Conflict of Interest Forms. Our DSMP will be included as part of the research protocol and submitted to the IUI IRB.

<u>Frequency of Data and Safety Monitoring.</u>

During the intervention phase of the R33 trial, nursing home Corporate Implementation Champions will be charged with asking nursing home based ACP Specialists about any adverse events and unanticipated problems that may have occurred in the course of their role. The nursing home Corporate Implementation Champions will meet at least monthly with the project team during the intervention phase. Any adverse events and unanticipated problems requiring immediate action will be discussed immediately with either of the PIs to determine necessary corrective action. Problems not requiring immediate actions will be addressed during monthly research team meeting and at quarterly DSMB meetings. Outcome of adverse events and unanticipated problems will be periodically reported to the IRB and the NIH.

<u>Content of Data and Safety Monitoring Report</u>

A Data and Safety Monitoring Report will be prepared once a year and will include status, participant descriptive information, safety information, and fidelity monitoring.

Data and Safety Monitoring Board Membership

DSMB membership will include experts or representatives of the field with relevant clinical expertise, clinical trials methodology, and biostatistics. The members will be selected by the National Institute on Aging (NIA) program officer in consultation with the Co-PIs.

Conflict of Interests

Members of the DSMB shall have no direct involvement with the study investigators or nursing home corporate partners. Each DSMB member will sign the IU Conflict of Interest Statement, which include current affiliations and any other relationships that could be perceived as a conflict of interest related to the study.

Protection of Confidentiality

Data will be presented in a blinded manner with no participant or nursing home identifiers. All materials, discussions, and proceedings of the DSMB will be completely confidential and DSMB members are expected to maintain confidentiality.

DSMB Responsibilities

The DSMB will be formed in consultation with the NIA program officer and will include 2-3 external members. According to NIA guidance, the Chair will be selected by the NIA. The DSMB Chair will serve as the safety officer for the project and will be responsible for running meetings. The DSMB will be charged with monitoring patient safety, data quality and overall performance of the study. Responsibilities will include review of the research protocol, with a focus on protecting patient confidentiality and the plan for data and safety monitoring. Review of performance will include progress towards milestones, evaluation of recruitment, assessment of any serious negative reactions, and identification of issues around data storage or quality. The DMSB will also advise the NIA on the readiness of the trial to initiate recruitment, progress of the trial, and review of study performance including making recommendations and/or assisting in the resolution of problems identified by the Co-PIs. The DMSB will report to the NIA on the safety and progress of the trial as well as commenting on any problems with study conduct, enrollment, sample size, and/or data collection. All adverse events and unanticipated problems occurring during the course of the study will be collected, documented, and reported to the PIs and the DSMB Chair. These will be reported to NIA Project Officer and IRB quarterly. The PIs will meet with the study team staff weekly and at least one of the Co-PIs will be available at all times via email or phone. Serious adverse events potentially related to the intervention will be reported to both the Chair of the DSMB and to the NIA Project Officer within 24 hours of either PI learning of the issue. The DSMB Chair will determine if an additional meeting of the DSMB is needed and convene.

8 INTERVENTION DISCONTINUATION

Adverse Event and Serious Adverse Event Collection and Reporting.

The potential *adverse event (AE)* that could occur during this trial is significant distress by patients or family members in the intervention NHs. Such events may be the manifestation of a very negative emotional reaction during a facilitated ACP discussion including uncontrolled crying or complaining to facility leadership. Due to the sensitive nature of the material, tearing up, crying, expressions of emotion, or early termination of the conversation by the proxy can be expected during advance care planning and are not deemed to be adverse events. The risk of potential distress caused by exposure to the ACP Specialist Program is no greater than the risk of distress from experiencing these conversations in routine clinical care.

Training of the ACP Specialist will include emphasis on the importance of asking permission to begin an ACP conversation and respecting patient and family refusals. It will also include provision of emotional support and empathic statements during discussions. ACP Specialist training will include recognition of AEs and instructions. In the R33 phase, staff will be instructed to report any negative reactions immediately to the Executive Director and the nursing home Corporate Implementation Champion. Instructions are provided to the ACP Specialists and Corporate Implementation Champions about what constitutes an adverse event. In the event of an AE, ACP Specialists will report the event to his/her immediate supervisor, who will report it to the Corporate Implementation Specialist. Together, these professionals will determine the severity of the event and if it is a true AE related to the ACP Specialist Program. If deemed necessary, the Corporate Implementation Champion will notify the research project staff within 48 hours of the event.

The project manager will report the AE to both co-PIs via email or telephone immediately upon becoming aware of the event and will also notify the TBN Data and Safety Monitoring Board (DSMB) Chair in writing (email and hard copy) within 48 hours. The Co-PIs will take ultimate responsibility for ensuring the DSMB chair is informed in a timely manner. Follow-up includes checking in with the patient or family caregiver within 6 to 24 hours of the initial AE to assess whether further intervention is needed to mitigate the AE. If necessary, the patient or family caregiver should be referred for follow-up (e.g., referring family caregiver to primary care provider or community mental health facility). A summary of any AEs will be reported quarterly to the NIA program officer and the IRB.

We do not believe any potential consequences of APPROACHES would be considered serious adverse events (SAEs). We do not believe that death should be considered an SAE for this trial as: 1) death is often not unexpected in this nursing home population with ADRD; 2) death is not an adverse outcome for patients and families with goals of comfort or palliation if those goals are met; and 3) it is not known whether or not aggressive care provided at the hospital results in lower mortality compared with conservative care in the nursing home.

In this pragmatic trial, we will work closely with the nursing home corporate partners deploying the intervention in order to monitor the overall safety of patients in the project, minimize any risk associated with the research, and protect confidentiality. After the initiation of the R33, the nursing home Corporate Implementation Champions and nursing home Corporate Data Experts from each of the 2 nursing home partners will participate in monthly meetings to discuss project implementation and address questions, problems, or concerns that might arise, including data safety and risk to patients.

Co-PIs Hickman and Unroe will continue to actively monitor for any results of other new research studies or regulatory policies that may have an impact on APPROACHES. Further, we will request the DSMB members to monitor for any external scientific or therapeutic developments that could impact the ethics of the trial or safety of participants.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The over-riding objective of this proposal is to conduct a pragmatic cluster-randomized controlled trial (RCT) of "Aligning Patient Preferences – a Role Offering Alzheimer's patients, Caregivers, and Healthcare providers Education and Support (APPROACHES)" that aims to improve ACP and goal-directed outcomes in nursing home patients with ADRD. In the R33 phase, we will conduct the full pragmatic RCT in partnership with 2 nursing home corporations (Signature HealthCARE and Miller's Health Systems) who operate a combined total of 142 diverse facilities in 8 states. Consistent with the spirit of a pragmatic trial, we will use existing data sources including electronic health records (EHR), the Minimum Data Set 3.0 (MDS), and Medicare Claims data to characterize the cohort and measure outcomes. Hospital transfers over 12 months among ADRD patients is the 1^{o} trial outcome.

9.2 Sample Size and Randomization

Power Calculations.

The implementational advantages of cluster RCT are gained at the expense of reduced analytical power, as compared to a simple RCT.[23] Reduction of power is proportional to the intracluster correlation (ICC) coefficient ρ, which represents the strength of correlation among subjects within the same cluster. The within-cluster correlation has a correlate – the between cluster variation, which is commonly expressed as the coefficient of variation (CV).[24] Larger ICC or CV values will lead to bigger variance inflation and more power loss.

A power analysis was conducted using preliminary data from the Minimum Data Set (MDS) provided by CMS. We estimated that the between-cluster CV would be less than 0.5. Assuming that the two treatment arms have similar CV values of a similar magnitude, we calculated the power for detecting 20% reduction in rate of hospital admission by the proposed intervention. Our analysis showed that with 120 facilities (60 per arm) and an average of 50 residents per facility, we will have 81% power to detect a 20% difference in the rate of hospitalization (1.0 per resident year in the control group vs 0.8 per resident year in the intervention group), by using a Poisson regression analysis

with 0.05 level of significance. We note that the power estimate is likely to be conservative because in the actual analysis, we plan to control for the effects of the covariates; the reduced variability explained by the covariates will increase the power.

9.3 Interim analyses and Stopping Rules

We will not be conducting an interim analysis or developing rules for stopping the trial early for several reasons. The planned intervention of a trained ACP Specialist who will augment usual care is unlikely to cause harm. The IRB has determined that this study is minimal risk. Particularly given the delay in obtaining Medicare claims for determining the primary outcome, hospitalization or emergency department visits, it will not be feasible to determine the differences in this outcome between the intervention and control groups until the end of the 12 month outcome observation period.

9.4 Outcomes

9.4.1 Primary outcome

9.4.1.1 Hospital transfers over 12 months among ADRD patients

9.4.2 Secondary outcomes

9.4.2.1 Hospice enrollment over 12 months among ADRD patients

9.4.2.2 Death in hospital over 12 months among ADRD patients

9.5 Data Analyses

Design consideration. The R33 phase of the study has two aims: (Aim 1 – Primary) To compare hospital transfers (admissions and emergency department visits) over 12 months between ADRD patients in the intervention and control facilities; and (Aim 2 - Secondary) assess the interventional effect of the ACP Specialist Program on hospice enrollment and place of death. Towards these ends, we employ a cluster RCT design. With this design, randomization will be carried out at the nursing home level, stratified by nursing home corporate ownership and baseline hospitalization transfer rates (low versus high). All patients at a given nursing home will have the same intervention assignment. The trial outcomes will be analyzed at the individual patient level and reported at the facility level. The cluster RCT with nursing home randomization is chosen because of its ability to simultaneously maximize the implementational feasibility and minimize the contamination risk.[25,26] Counts of hospital transfers and emergency department visits incurred by individual ADRD patients during the follow-up period will be considered as the primary outcome. We designed the trial to ensure adequate power for the hypothesis concerning the primary outcome. Average age and proportion of female patients is similar across our nursing home partner facilities and the U.S. The % of Black patients ranges from 6-17% across the population of our partner nursing homes. About half of nursing home patients have a dementia diagnosis. This is similar for our partner facilities.

Analysis will be carried out in an intention-to-treat (ITT) framework, which gives a pragmatic estimate of the interventional benefit.[27] The ITT analysis will use data from all eligible patients in randomized facilities, regardless of the level of facilities' adherence to the study protocol and patient attrition. ITT is a preferred approach for pragmatic trials

because the analysis generates estimates of treatment effectiveness in a more realistic way. In fact, clinical effectiveness can be severely overestimated if ITT analysis is not performed.[28] Within the ITT framework, we propose to analyze the trial data using appropriate generalized linear models. Specifically, we plan to compare the rates of hospital admissions in patients residing in the intervention vs control facilities. In line with intention-to-treat principles and our cluster randomized design, hospitalizations will be analyzed at the facility level, including for residents who moved across intervention and control buildings during the study period. Group assignment will be based on the facility each resident was first admitted to during the intervention period. Thus, some residents may have a documented ACP encounter in intervention facilities but also spent some time in control facilities. The analysis will be carried out using an appropriate count data regression model, length of observation will be adjusted as an offset parameter. We will test the levels of extra-Poisson variation to determine if a Poisson regression model is sufficient for the analysis. If the level of variation is beyond what can be accommodated by the Poisson model, we will consider using negative binomial regression. Similarly, we will test the presence of extra zeros that beyond the Poisson or negative binomial models. If necessary we will consider the use of zero-inflated Poisson or negative binomial regression analysis. Correlations among outcomes measured from residents in the same facility will be accounted for by adding random facility effects into the regression models. This analytical approach handles missing data (early dropout due to death or transfer to hospice) more easily because of the inclusion of offsetting parameters in the model.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Management

The proposed study will combine multiple sources of patient data to measure impact on the quality of care near the end-of-life.

10.2 Quality Assurance

10.3.1 Training

ACP Specialists will complete standardized training via modules created for the study and available in their learning management systems. Corporate representatives and corporate implementation champions will complete a corresponding training adapted for key leaders via modules created for the study and available in their learning management systems.

10.3.2 Quality Control Committee

Not applicable.

10.3.3 Metrics

Provide quality control metrics for outcome measures.

10.3.4 Protocol Deviations

Protocol deviations will be assessed in monthly meetings with the corporate implementation champions. Since this is a pragmatic trial, we anticipate and have built-in flexibility in implementation of the ACP specialist program that would not be considered a protocol deviation.

10.3.5 Monitoring

Monitoring will occur via review of the monthly data transfer and through monthly meetings with the corporate implementation champions.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The proposed study has been reviewed by the Indiana University Institutional Review Board (IRB), which will serve as the centralized, single IRB for the trial in accordance with National Institutes of Health policy. This trial is registered at clinicaltrials.gov (NCT03323502). A Data Safety and Management Plan is described in this protocol.

11.2 Informed Consent Forms

A wavier of informed consent was sought from the IRB. This pragmatic clinical trial meets the criteria for a waiver of informed consent as described in 45 CRF 46:116. Specifically: 1) this research represents no more than minimal risk; 2) a waiver does not adversely affect the rights and welfare of participants; 3) the research could not be practicably carried out without the waiver; and 4) information will be provided to the nursing home partners after the trial to share with interested patients and family caregivers.[29] Patient and family caregiver refusals to participate in ACP discussion will be honored.

11.3 Participant Confidentiality

Data provided by nursing home corporate partners (MDS, EHR) will be transferred using HIPAA compliant, encrypted processes. CMS (Claims, MDS) and EHR data files will be securely stored using processes developed to meet CMS data requirements as part of a prior CMS data request. Specifically, data will be stored on a virtual server administered by Indiana University's Clinical Affairs IT Service (CAITS) team. The virtual server is located on Indiana University's Intelligent Infrastructure on hardware that is physically located in two enterprise-class machine rooms in separate physical locations. The server rooms require biometric authentication in addition to a chip-based access card and are staffed 24x7x365 and feature video security. Network firewall rules are used to restrict server access to only necessary subnets. Only IU domain workstations with security controls (auto logoff, centralized threat management, host-based firewall, and more) will be permitted to connect to the virtual server. Each study team member with access to the CMS data must use a passphrase. Protocols are in place dictating that passphrases must be at least 15 characters in length with at least 4 unique characters (letters, numbers, and symbols) and use at least 4 words separated by spaces or other non-letters. Password reuse is restricted, not allowing the previous 2 passwords to be reused. Sessions on workstations and servers, whether local or remote, are locked after being idle for 15 minutes and terminated after 24 hours of non-use.

The systems used to store and analyze the data will be subjected to a documented NIST-based risk management process prior to receipt and use of the requested data. The process is briefly outlined below:

a) Inventory assets—hardware, software, personnel.

b) Document controls—identify every existing and appropriate NIST 800-53 control for the system. NIST 800-53 (an industry and government standard) is a comprehensive catalog of 926 security controls. NIST 800-66 (a mapping of the HIPAA security rule to NIST 800-53) is used to identify appropriate controls for electronic Personal Health Information.
c) Assess risk—identify risks that existing control address and residual risk from missing controls.
d) Respond to risk-how each residual risk is addressed (mitigated, transferred or accepted), explanation/justification, and timelines for mitigation, if any.
e) Establish ongoing risk management—semi-annual reviews and documentation updates, external assessments.
f) Training-two annual HIPAA training courses (University general course and an IT-specific course).

11.4 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.

12 ETHICAL CONSIDERATIONS

Protections against Risk

Informed consent will not be sought from patients or family caregivers for this pragmatic cluster randomized control trial.[30] Strategies to minimize risk to participants are based on the experiences of the study PI and Co-Is in conducting research on ACP and in the nursing home setting. Additionally, Dr. Hickman has expertise in ethical issues in research with these populations to inform both study design and strategies to protect against risk. Dr. Hickman has previously conducted research on ethical issues in conducting long-term care research[31,32] and NIH-funded research on ethical issues in end-of-life research.[33]

13 COMMITTEES

Executive Committee: The Executive Committee will oversee all aspects of project development, implementation, and analysis including human resources, communications with the National Institutes of Health, and budgetary decisions.

Steering Committee: The Steering Committee will include the Co-PIs Hickman and Unroe, Co-I Tu, Consultants Mitchell and Hanson, and representatives from each nursing home corporate partner. This group will be responsible for overseeing the project direction, ensuring close collaboration between APPROACHES and nursing home partners, coordinating workgroup tasks, and meeting project milestones. This includes transition to the R33 phase. The Steering Committee will also be responsible for reviewing EHRs to ensure existing fields adequately capture relevant ACP data to guide clinical care (e.g., allow for documentation of specific POLST form orders and not just code status) with the goal of standardization of documentation across sites and the creation of clinically useful dashboards.

Regulatory and Operations Workgroup: This workgroup will be led by Co-PI Hickman, with Co-PI Unroe, the project manager, data manager, information technology (IT) support, and nursing home Corporate Data Experts. This Workgroup will be responsible for obtaining signed Memoranda of Understanding as well as a signed Data Use Agreements (DUA) from each corporate nursing home partner and ensuring data are transferred safely. This Workgroup will prepare and submit the CMS data request outlining all data security precautions along with related institutional policies. Because of the close link between data security and issues related to patient and family caregiver confidentiality, this workgroup will be responsible for oversight of the human subjects' protections. This included submitting an application to the Indiana University Institutional Review Board (IU IRB), which will serve as the IRB of record, and requesting a waiver of informed consent for patients and family caregivers. Finally, this group will oversee the implementation of the Data Safety and Monitoring plan, which includes developing the Data Safety and Monitoring Board (DSMB) charter, convening the DSMB, and supporting its work (see Section F).

APPROACHES Intervention Protocol Workgroup: This group will be responsible for implementation in the R33 phase. It will be led by Co-PI Hickman with Co-PI Unroe, Consultant Hanson, the Project Manager, and representatives from the partner organizations.

The ACP Specialist Program is based on the successful OPTIMISTIC nurse role but adapted for use by internal nursing home staff. The ACP Specialist Program will be implemented as a new nursing home initiative. Corporate policies regarding ACP practices will be reviewed and potentially modified or developed in collaboration with our nursing home partners to support roll out of this new initiative. Signature HealthCARE and Miller's Health Systems corporate leadership have expressed willingness to make policy or procedure modifications necessary to support the ACP Specialist Program. Similar to OPTIMISTIC, a process will be developed to ensure the staff member designated as the ACP Specialist is assigned a group of 10 ADRD patients each month to approach about ACP with accountability for reporting to local nursing home leadership. The intervention will be refined in collaboration with nursing home partners and current OPTIMISTIC nurses. Any modifications will be based on consensus, and rely on national standards and existing evidence from research. Meetings will first be held separately with Signature HealthCARE and Miller's Health Systems corporate leadership to identify opportunities and potential barriers within each system. The program will be refined based on this feedback followed by a smaller, combined meeting with representatives from each organization to review and finalize.

The ACP Specialist Program includes a brief online training for Executive Directors, Medical Directors, and Directors of Nursing (approximately 1 hour for each). The materials have been tailored to each nursing home corporation electronic learning platform and brand standards. The goals of this training are: a review of ACP and its importance, particularly for patients with ADRD and their families; an understanding of the ACP Specialist Program and role; and to convey the importance of support for the ACP Specialist dedicated role as a key nursing home staff position. Nursing home

leadership will be expected to offset the ACP Specialist's new responsibilities by permanently shifting work to other staff.

The nursing home staff member designated as the ACP Specialist will complete a longer training (approximately 7 hours) and will receive a hard-copy manual including sample, educational handouts and access to videos for patients, families, and other nursing home staff, documentation instructions, tracking tools, and tips for navigating common barriers. Due to the COVID-19 pandemic and its significant impact on NHs, an Introductory Launch Course was created for ACP Specialists to complete prior to implementation at their facility with the understanding that all additional training modules would then be completed. The training will include specific information about decision-making for patients with dementia. Training materials are anticipated to include OPTIMISTIC educational tools created by Dr. Hickman and materials developed by Dr. Hanson. Core expectations include review and modification of ACP procedures as needed, education provided to other nursing home staff, and dedicated time to coordinate and facilitate ACP discussions with ADRD patients and/or family caregivers using the target assignment list. Based on experience with OPTIMISTIC, the ACP Specialist will require a minimum of 1 day per week (20% FTE) initially, with a reduction over time after the initial start-up work. Dedicated time and schedule flexibility are critical to the success of the ACP Specialist to reach family caregivers and facilitate conversations.

Consistent with the principles of a pragmatic trial, instructions about how to implement the protocol role will be highly flexible.[34] For example, some facilities may decide to train more than one ACP Specialist within the building to share responsibilities. There is also flexibility in level of expertise required by practitioners delivering the intervention so the ACP Specialist may be any staff person deemed qualified by the nursing home Executive Director to fulfill the role, though it is anticipated it will likely be a social worker or a nurse. It is expected that there will be adaptations to the ACP tools and educational materials as needed.

Data Management and Analysis Workgroup: This group will be led by Co-PI Unroe with Co-I Tu, Co-PI Hickman, Co-I Mitchell, biostatistician, data manager, and IT Support. This group is responsible for the data management required to link data sources in preparation for analysis as well as the analysis itself. In order to assess our outcome measures to both justify the adequacy of these measures and finalize these variables, a subset of MDS and Claims file records will be compared to the nursing home EHR in collaboration with our clinical partners to determine whether the process of merging was accurate. For example, validity checks will be performed to see if all hospital transfers are captured.

14 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. Publication authorship will be based on the relative scientific contributions of the PIs, key personnel, and nursing home corporate partners (e.g., nursing home Corporate Implementation

Champion).

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