# Indiana Palliative Excellence in Alzheimer's Care Efforts-Randomized Control Trial
# Protocol

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## 1.0 Background

**Dementia is an increasingly prevalent, costly and burdensome condition.** The dramatic aging of the US population is creating a dementia "epidemic" that our health care system is poorly prepared to handle. More than 5 million people are affected by Alzheimer's disease (AD) and related dementias in 2016, with that number estimated to nearly triple to 13.8 million by 2050. The direct health care costs alone for dementia care are projected to increase from $236 billion in 2016 to more than $1 trillion in 2050. In addition to cognitive and functional deterioration, patients with dementia experience behavioral and psychological complications such as agitation and depression. Family caregivers of patients with dementia experience higher levels of anxiety, depression, chronic fatigue, and an increased mortality risk.

**Dementia and palliative care are national research priorities.** Both dementia and palliative care have been identified as priority conditions for research and quality improvement by numerous organizations such as the Institute of Medicine, National Quality Forum, the Centers for Medicare and Medicaid Services, and Agency for Healthcare Research and Quality and NIA. In addition, a workgroup developing milestones for care and support under the U.S. National Alzheimer's Plan has explicitly stated that palliative care needs to be incorporated throughout the course of caring for patients and families affected by dementia.

## 2.0 Rationale and Specific Aims

**Aim 1: To test the effect of the IN-PEACE intervention on patients' neuropsychiatric symptoms (e.g., agitation/aggression, anxiety, repetitive behaviors).** Mixed effects models will be used to compare repeated NPI-Q scores obtained at 3, 6, 9, 12, 15, 18, 21, and 24 months. Repeatedly measured NPI-Q scores will be the dependent variable in the model.

**Aim 2: To test the effect of the IN-PEACE intervention on patients' overall symptom outcomes.** Analyses in this aim will use repeatedly measured SM-EOLD scores over 24 months of follow-up as the dependent variable in the mixed effects model, similarly to the approach described for Aim 1.

**Aim 3: To test the effect of the IN-PEACE intervention on caregivers' distress and mood.** Aim 3 analyses will use repeatedly measured caregiver NPI-Q distress scores and caregiver PHQ-9 over 24 months of follow-up as the dependent variables in separate mixed effects models, similar to the approach for Aim 1.

**Aim 4: Evaluate the effect of the IN-PEACE intervention on ER/hospital use.** ER/hospitalization events will be obtained from accessing electronic medical records maintained by the Indiana Health Information Exchange (IHIE) and the Indiana Network for Patient Care (INPC). Poisson regression models will be used to compare rates of any ER/hospitalization event between the two groups while adjusting for dementia severity and significant baseline variables that differ between the two groups.

## 3.0 Inclusion/Exclusion Criteria

We will recruit a total of 225 patient-caregiver dyads, randomizing 112 dyads each to the intervention and control (usual care) arms.

Eligibility criteria for patients include:

- age 65 or older
- community-dwelling in the Indianapolis metropolitan area (assisted living facility acceptable; long stay NH residents excluded);
- have an established diagnosis of dementia of any etiology as determined by memory care practice and confirmed by research team review of medical record;

- dementia in the moderate (FAST stage 5) to severe stage (FAST 6-7); and
- have a primary caregiver available and willing to serve as both an informant on the patient's status and as a subject him or herself.

Exclusion criteria for patients include:

- resident living in a nursing facility, Skilled Nursing Facility, Long Term Acute Care (LTC), Personal Care Home
- patient expressing dissent
- being diagnosed with a serious mental illness such as bipolar or schizophrenia
- Hospice enrollment (Addition IRB Approved: 5/13/2019)

Eligibility criteria for caregivers include:

- reside locally;
- English-speaking;
- live with patient or have at least 2 contacts per week on average with the patient (1 face-to-face);
- designation as the patient's primary caregiver; and
- has not been diagnosed with a serious mental illness such as bipolar or schizophrenia.

*Recruitment*

Dyads will be recruited from Indiana Discovery Network for Dementia (http://indydiscoverynetwork.org/) memory care practices in the Indianapolis area. Utilizing established memory care practices allows us to rely on their diagnostic assessment (confirmed by record review by research team) and to efficiently recruit eligible subjects. Our customary and successful recruitment methods utilize the Indiana Network for Patient Care (INPC) and the Indiana Health Information Exchange (IHIE) to identify potentially eligible patients with dementia based on ICD-9 and ICD-10 diagnostic codes and prescriptions for anti-dementia drugs in medical records. Memory care providers then help narrow the list of potential dyads to be approached and allow access to clinic schedules. Research assistants then arrange to meet dyads at a clinic appointment or offer a home visit to discuss the study.

Research staff will ask caregivers a series of questions to assess the patient's cognitive and functional status. This information will be used to determine the severity of the patient's dementia using the FAST. Only patients meeting criteria for FAST stage 5 (moderately severe) or stage 6-7 (severe) will continue in the enrollment process.

An IN-PEACE research assistant, with approval from the practitioner, will obtain informed consent of the patient's legally authorized representative (LAR) for study participation. (The LAR and caregiver will be two individuals in a few cases. For example, one adult child may hold power of attorney for the patient and another adult child may be the primary caregiver. In those cases, the LAR gives proxy consent for the patient and the caregiver gives informed consent for their own participation.) Because the severity of the patient's dementia is advanced, while decision making capacity of the patient will be assessed using the teach-back method, we expect most patients will lack decisions making capacity to provide informed consent If the patient expresses meaningful dissent, patient will not be enrolled, even if the LAR is willing to consent.

Potential subjects can self-refer for this study. Approved study brochures will be distributed at community events, such as conferences, meetings, or other contacts with the public. Interested subjects will be asked to provide their name, email address, telephone number and mailing address. A Research Assistant will contact potential subjects with the contact information provided to screen for inclusion/ exclusion criteria to determine eligibility. We may email/ direct mail consent statement to interested participants, upon request. The mail/email template will include the scripted language previously approved with the screening/ enrollment script, and approved IN-PEACE brochure. An Email/Direct mail template has been approved by the IRB.

## 4.0 Enrollment/Randomization

After enrollment and baseline assessments are completed, subjects will be classified according to disease severity (moderately severe (FAST = 5) or severe (FAST = 6-7).

Stratified randomization based upon dementia severity will be used to assign patient-caregiver dyads to either the intervention or usual care arm.

## 5.0 Study Procedures

### *Timeline*

The study will take place over five years with a six month start-up time period. It will take 24 months to accrue the target sample size utilizing a rolling enrollment and intervention delivery process. Subjects receive the intervention for 24 months and the last outcome assessment is also at 24 months. In the final year of the study, in addition to completing analyses and preparation of manuscripts, we would plan a competitive renewal proposal to continue following the subjects in order to address aims relating to care in the last days/weeks of life, hospice referral, and resource utilization.

| | YEAR 01 | YEAR 02 | YEAR 03 | YEAR 04 | YEAR 05 |
|---|---|---|---|---|---|
| Start-up activities | | | | | |
| Subject accrual | rolling enrollment over 24 months | | | | |
| Intervention Delivery | each dyad receives 24 months of the intervention | | | | |
| Outcome assessments | each dyad assessed at baseline, 3, 6, 9,12, 15, 18, 21, and 24 months | | | | |
| Analysis; manuscripts | | | | | |

### *Assessments: Measures and Schedule of Administration*

| Domain | Measure | Items | Schedule (months) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 | EOL |
| **Patient (PT) measures** | | | | | | | | | | | | |
| **Patient related measures assessed directly by research assistant** | | | | | | | | | | | | |
| Cognition | MOQA | 30 | X | | | | X | | | | X | |
| **Patient related measures obtained via caregiver (CG) interview (proxy report)** | | | | | | | | | | | | |
| Neuropsychiatric Symptoms | Neuropsychiatric Inventory Questionnaire (NPI-Q)[91] | 12 | X | X | X | X | X | X | X | X | X | |
| Symptom Management | Symptom Management at the End of Life in Dementia (SM-EOLD)[92] | 9 | X | X | X | X | X | X | X | X | X | X |
| Comfort Assessment | Comfort Assessment in Dying with Dementia (CAD-EOLD)[92] | 15 | | | | | | | | | | X |
| | | | | | | | | | | | | |
| Activities of Daily Living | Physical Self-Maintenance Scale[106] | 13 | X | X | X | X | X | X | X | X | X | |
| Functional status | FAST staging[80] (caregiver report, ADLs) | | X | | | | | | | | | |
| Medical comorbidity | Checklist of conditions[11] | 10 | X | | | | | | | | | |
| | | | | | | | | | | | | |
| **Caregiver measures from CG interview** | | | | | | | | | | | | |
| CG Distress from Neuropsychiatric Symptoms | Neuropsychiatric Inventory Questionnaire (NPI-Q)[91] (CG reaction portion of instrument) | 12 | X | X | X | X | X | X | X | X | X | |
| Depression (CG) | Patient Health Questionnaire (PHQ-8)[65] | 9 | X | X | X | X | X | X | X | X | X | X |
| Caregiver Strain | Caregiver Strain Index[107] | 13 | X | | | | X | | | | X | |
| Satisfaction with Care | Satisfaction with Care at the End of Life in Dementia (SWC-EOLD)[92] | 10 | X | X | X | X | X | X | X | X | X | X |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Respondent Burden | Benefit and Burden Scale[108] | 4 | | X | X | X | X | X | X | X | X | X |
| **Other data from CG interview** | | | | | | | | | | | | |
| Advance Care Planning (ACP) | Questions on specific directives | 10 | X | X | X | X | X | X | X | X | X | |
| Hospice | Hospice utilization | 4 | | | | | | | | | | X |
| Socio-demographics (PT/CG) | age, race, sex, education, marital, job status, income | 10 | X | | | | | | | | | |
| **Medical Record Review and INPC/IHIE Data Stream** | | | | | | | | | | | | |
| Etiology of Dementia | Chart review | n/a | X | | | | | | | | | |
| ER/Hospitalizations | Health information exchange data | n/a | | | | | X | | | | X | X |

***Intervention***

**Intervention arm.** Multi-disciplinary clinical team meetings with PI, co-investigators (MA, KK, SH, AMT), and care coordinators will be held weekly throughout the study. During these meetings, the team will review data from the baseline assessments to

- identify triggers for interventions,
- make protocol and other treatment recommendations, and
- communicate these to the care coordinator for dyads randomized to the intervention arm.

Caregivers will be contacted by the care coordinator within one week following the clinical team meeting or within ten days of the baseline assessment.

Care coordinators will initiate caregiver protocols to address unmet needs and individualized areas of focused care, overcoming barriers to provision of excellent palliative care. The assigned care coordinator will be the primary contact and will follow the dyad throughout the study with backup support and cross-coverage (i.e. social worker may call in RN for help with nursing issues and vice versa).

The coordinator will direct the caregiver to the INPEACE manual (provided at enrollment that contains PREVENT materials relating basic dementia care needs, caring for the caregiver, management of neuropsychiatric symptoms, and the IN-PEACE materials on goal setting and advance care planning, pain evaluation and management, navigating the hospital, feeding difficulties, and hospice transitions, including appropriate industry materials). Specific tools to aid in the evaluation and management of pain include a list of nonverbal indicators of pain[77] and a card with the Iowa Pain Thermometer[78] on one side and Faces Pain Scale[81] on the other. These will aid in rating pain and in communicating about it with the care coordinators and physicians. Caregivers will be instructed that they can refer to the management techniques in the manual on their own and should have it available when speaking with the care coordinator on the phone. Caregivers will be asked to contact the IN-PEACE care coordinators throughout the study at times of acute events or symptom changes, hospitalization, or with questions, concerns, and referral/resource requests.

Care coordinators will record information on all contacts and interventions in templated notes in the web-based tracking system, both to provide information for follow up, as well as to provide descriptive information on numbers and types of contacts, protocols triggered, and interventions carried out.

Care coordinators will initiate contact with caregivers at 1, 2, and 4 weeks after enrollment and then monthly thereafter. At each contact, the DCC will use, open-ended questions about the patient's most bothersome symptoms, and the caregiver's assessment of the patient's level of pain. Responses indicating symptoms that are frequent or causing distress in the patient or caregiver trigger the appropriate protocols for managing those symptoms. Non-pharmacological and behavioral strategies have an early and important role in the protocols. Several of the protocols have the equivalent of laboratory "panic values," findings that would trigger a more intensive response from the care coordinator. For example, new onset pain that is severe would result in a call to the patient's primary care physician and discussion about whether the patient should be seen in the office or even the emergency room. Some of the protocols may trigger follow up sooner than the next scheduled

monthly contact. Using pain as the example again, the care coordinator will contact the caregiver within 72 hours and continue to intervene if there has not been at least a 50% reduction in the rating of pain.

Some protocols, such as feeding/weight loss and planning for hospice, may be triggered either by a decline in functional status or a hospital admission, rather than a symptom. Goal setting and advance care planning will be addressed repeatedly, first at enrollment and then as major changes in clinical status occur. The clinical team will meet weekly with the care coordinators to discuss scheduled contact reports, caregiver initiated contacts and questions, and review and revise plans of care. Recommendations of the clinical team will be tracked in the care coordinator's contact database with follow up appointments set. For more urgent medical issues, care coordinators can contact the clinical team representative between meetings for advice or recommendations to the caregiver to seek care from the primary care provider or emergency room.

Table 2 outlines barriers to palliative care in dementia, possible solutions, and the aligned protocols developed for IN-PEACE to address the barriers.

Table 2: Palliative Care in Dementia: Barriers and Solutions

| **Barrier to excellent palliative care in dementia[82]** | **Potential Solution(s)** | **IN-PEACE Protocols/Interventions** |
|---|---|---|
| "Dementia not a terminal illness" | Reframing advanced stages as terminal | Prognostic Information |
| Lack of advance care planning | Ongoing care planning with caregivers | Goals of Care / Advance Care Planning |
| Poor symptom management | Proactive assessment and attentive management | Proactive Assessment (behaviors/psychological; pain; other symptoms; caregiver mood/distress)<br>Symptom Protocols<br>Caregiver Support Protocols |
| Difficult decisions: antibiotics and tube feeding | Information about benefits & burdens; context of goals of care, alternatives | Goals of care / Advance Care Planning<br>Feeding / Weight Loss<br>Navigating Hospital |
| Avoidable hospital use<br>Burdensome treatments/transitions<br>Underutilization of hospice | Support care at home<br>Increase discussion of benefits of palliative care and hospice options | Symptom Protocols<br>Goals of Care / Advance Care Planning<br>Transition to Hospice |

The information collected by the care coordinators via telephone that are either scheduled or initiated by caregiver concerns at any time will be reviewed at weekly interdisciplinary team meetings. This information will consist primarily of reports of behavioral problems, pain and other bothersome symptoms, and caregiver well-being. <u>This "clinical data" is used solely to help manage care of the patient and caregiver and are not part of the separately scheduled research outcome assessments.</u> The team also will review any interventions carried out or ordered by the care coordinator, additional services recommended, and assess initial responses to these actions, if already available. The team may further modify the care plan.

The two Research Assistants will be blinded to the randomization assignment and will not be involved in any meetings or discussions about intervention subjects. The research manager (LH) will review outcomes measures and if there are any values that exceed pre-specified levels, she will bring those to the attention of the PI. These are similar in nature to "urgent" or "panic" values in laboratory blood test reports or X-ray reports requiring attention of a clinician and represent a safety feature for all dyads, control and intervention, and not a part of the IN-PEACE intervention. For example, any severe pain or pain associated with a fall or other trauma will result in a call to a physician and either scheduling of an appointment or instructions to go to the emergency room.

The revised plans of care generated by the care coordinators and the supportive care clinical team are intended to affect the study outcomes and should be thought of as integral components of the

intervention. Tailoring protocolized treatment actions to the particular patient's needs is the standard for multi-component trials of collaborative care interventions.

The care coordinators will send periodic updates, in the mode and frequency as requested, to the patient's primary care provider. Most participating providers in the Indianapolis area will be familiar with electing secure email, fax, phone, or text pager for their preferred modes of communication because of the INPC, IHIE, and other ongoing, innovative efforts, such as those sending pending lab results from hospital and emergency room visits to physicians' offices. The team will communicate with the primary care provider to request referrals to other specialists and when initiating protocols such as pain and hospice conversations.

Additionally, up to 25 caregivers, randomized to the intervention arm, will be asked to participate in a one-time qualitative interview aimed to explore the attitudes toward and experience with decisions to deprescribe medications of caregivers for community dwelling patients with moderate-severe AD with a focus on learning from the caregivers the ethical considerations that they take into account. The study will employ semi-structured interviews (in-person or by telephone) and qualitative methods for analyzing transcriptions of the recorded interviews.

**Usual care arm.**

Dyads randomized to "usual care," will be receiving care that is likely of a higher quality than the typical patient with dementia in the community setting given the involvement of IDND memory care practitioners. However, control dyads will not have access to the dementia care coordinator proactively making contact, assessing needs, and implementing IN-PEACE management protocols as the intervention subjects will have. Caregivers in the usual care group will have access to educational and informational materials from the local chapter of the Alzheimer's Association and other community resources and will be reminded of their availability. Protocols will be in place for appropriate referral when research assistants' assessments elicit information about severe symptoms or distress.

**Data Collection**

Baseline and final outcome assessments will be done in person at the subjects' home or the memory care practice site. Other outcome assessments will be done by phone or in the home, based on caregiver preference. The outcome measures for both intervention and usual care groups will be collected at baseline and months 3, 6, 9, 12, 15, 18, 21, and 24 post-enrollment. Caregivers also will be interviewed 6 to 8 weeks after the patient's death if that occurs during the course of the study. Data will be collected by research assistants who have not been involved in the ongoing management of the patients and are blinded to dyad assignment to intervention or usual care arm.

Data obtained from the one-time qualitative interview will be audio-record and transcriptions will be used for data analysis using grounded theory.

## 6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The safety monitoring for this study will be the responsibility of the Principal Investigator (Sachs), study biostatistician (Gao), and Safety Officer, who is external to Indiana University, and who are knowledgeable about dementia and older adults. Specifically, the Safety Officer will be selected based on the knowledge and experience in dementia, caregiving, palliative care, and clinical research studies. The Safety Officer, PI, Program Officer, and study biostatistician will meet by phone semi-

annually during active recruitment, data collection and analysis. Topics the group will review include: inclusion/exclusion criteria; participant accrual; and adherence and modifications to research protocols and procedures. Preliminary data trends on the primary and secondary outcomes will be discussed. In addition, the group will review procedures for protection of human subjects, including study withdrawals and adverse events reports and devise stopping rules, as applicable, based on potential harms and adverse events.

## 7.0 Study Withdrawal/Discontinuation

Subject withdraws, and adverse events will be reviewed by the Safety Officer, PI, Program Officer and study team members at the semi-annual meeting, or as prescribed in the Data Safety and Monitoring plan.

## 8.0 Statistical Considerations

The proposed study is a RCT comparing the multi-component, supportive care intervention (IN-PEACE) to usual care. Primary and secondary outcomes will be collected at baseline, 3, 6, 9, 12, 15, 18, 21, and 24 months. A patient reaches study endpoint by either completing 24 months of follow-up or other conditions described in Subject tracking. We will compare baseline characteristics between the intervention group and the control group using two sample *t*-tests for continuous normally distributed variables, Wilcoxon test for continuous non-normal variables, or chi-square tests for categorical variables. Variables found to be significantly different at the $\alpha$=0.05 level will be adjusted in the comparisons of all outcome variables.

Table 4: Power estimates for significant interactions between group and time in the mixed effect models with 85 patients per group.

| Outcome Measures | Expected Change in Outcome (3-month interval) | | Power |
|---|---|---|---|
| | Intervention | Usual Care | |
| Aim 1: NPI-Q Severity | -0.45 | 0.2 | 80% |
| Aim 2: SM-EOLD | 1.31 | 0* | 85% |
| Aim 3a: Caregiver NPI-Q distress | -0.39 | 0.08 | 80% |
| Aim 3b: Caregiver PHQ-9 | -0.22 | 0.16 | 81% |

## 9.0 Privacy/Confidentiality Issues

We will also take great care in assuring data security. Perhaps the most important element of data security is proper training of the scientists and their staff in research involving human subjects and in privacy and confidentiality. Data are handled only by research staff with specific training in data privacy and confidentiality. Data are stored on a secured workstation that is in a locked office within a locked suite of offices and the workstation and files are password protected. On rare occasions when data are to be transferred from secured workstations to one of the investigators' workstations for further analyses, the transferred dataset will be stripped of unique identifiers (de-identified dataset) including SSN, name, address, dates, and any personal identifiers. This is standard operating procedures for our work with research data. In addition, Regenstrief Institute databases and individual workstations are protected from unauthorized remote access by a sophisticated firewall which is tested on a regular basis. Data presented in reports are always reported in aggregate and never contain personally identifiable health information.

## 10.0 Follow-up and Record Retention

The study is scheduled for 24 months. Records will be maintained in secure location and will be retained as required per regulations.