STATISTICAL ANALYSIS PLAN

Version Date: 3/12/2024

NCT04837937

Aim 2: *Utilizing Multiphase Optimization Strategy (MOST), conduct a randomized pilot trial of the NDR intervention that targets better communication between caregivers and health teams, using a 23 full factorial design, to (2a) determine the feasibility of delivering the intervention, and (2b) derive estimates of the effect of 3 intervention components on changes in patient-centered outcomes at post-intervention and follow-up.*

Exploratory Aim 3: *Explore if intervention components (lectures/exercises) interact to change communication between caregivers and health care teams at post-intervention and follow-up.*

Research Design: Randomized Pilot Trial (Aims 2 & 3). Aim 2 will use a 2^3 full factorial trial design to test 3 binary components. Individuals will be randomized to 1 of 8 experimental conditions (**Table 1**). As shown in Table 1, participants can be assigned to intervention ("Yes") or control ("No") conditions *for each component*. Participants will be blinded to their experimental condition, but everyone will receive "caregiver-patient" negotiation exercise so that no participant gets an inactive placebo.

Table 1: Full Factorial Design

Experimental Condition	NDR Exercises by Relationship Conflict Content			
	Caregiver - Patient – Easy [Constant]	Caregiver-Caregiver	Caregiver-Physician	Caregiver - Patient – Difficult
1	Yes	No	No	No
2	Yes	No	No	Yes
3	Yes	No	Yes	No
4	Yes	No	Yes	Yes
5	Yes	Yes	No	No
6	Yes	Yes	No	Yes
7	Yes	Yes	Yes	No
8	Yes	Yes	Yes	Yes

Unlike the two-arm RCT, *the factorial trial compares combinations of conditions* to test main effects of and interactions between exercises. For example, to test the main effect of the NDR exercise between caregiver-physician, conditions 1-4 are compared to conditions 5-8 (see **Data Analysis**). In this way, participants are "recycled" across conditions to contain the sample size.

Participants & Recruitment. We will plan to enroll 130 family caregivers in the study.

Procedure & Randomization. Interested individuals will complete a brief screen by telephone to assess potential eligibility. Potentially eligible individuals will be screened and invited to enroll in the intervention and consent using e-Consent. Randomization will be performed using study-ID embedded URL links a-priori to assign participants to an experimental condition with an 8:1 ratio.

Survey Time Points. Subjects will be asked baseline questions by phone prior to initiation of the intervention. After the NDR training is complete, subjects will automatically be provided an electronic survey. Subjects will then be contacted at 1 and 3 months (+/- 2 weeks) through their email to completed follow-up surveys electronically (Table 2). We chose time-points of 1 month to gain information on the NDR training and 3 months for sufficient time for caregivers to utilize the information presented in the NDR training and detect changes in outcomes.

Table 2: Study Components, Time-Points

Intervention			Follow-Up Surveys	
Baseline Survey (T1)	Intervention Completion	Post-NDR Survey (T2)	1 Month (T3)	3 Month (T4)

Assessments. During the initial assessment, research staff will collect baseline variables that map to the Conceptual Model of Negotiation, specifically to Contextual Factors of the Negotiator and Structural. These include:

Demographics. information on the caregivers subject (e.g. gender, education, work experiences) as well as proxy demographics of the care recipient with AD.

Intervention-Centered Outcomes. We will assess feasibility of the NDR training with caregivers through assessments of a) Study Recruitment Rates (# of people), b) Study Retention Rates (# of people), c) Completion of NDR Training Exercises and d) Acceptability (System Usability Scale [a 10-item measure of usability] [105,106] and the USE Scale [a 30-item measure of usefulness, satisfaction, ease of use, and ease of learning]).[107] A multiple choice questionnaire will be conducted to ascertain knowledge of negotiation strategies. After the intervention and in follow-up months, participants will complete a brief, semi-structured interview to assess perception of the assigned intervention program, satisfaction, and progress, with both Likert scales and open-ended questions to obtain qualitative data.

Patient-Centered Outcomes. As this proposal seeks to tailor and test a novel NDR intervention to improve the lives of family caregivers, the primary outcome will be Positive Affect and Well-being. The Positive Affect and Well-Being (Neuro-QOL PAW)[118] measure was designed to aid clinicians and researchers to better evaluate and understand the potential role of positive health processes for individuals and has been previously validated. This choice was supported as its development emphasized the importance of early qualitative input from neurology professionals, patients, and caregivers. In development of the Neuro-QOL, interview and focus group participants spontaneously reported positive responses to chronic illness,

including themes of spirituality, meaning, mastery, and control, which provided the most important issues facing caregivers. The extensive care needs of individuals with AD are variable, and care typically involves great demands on spouses and other family members.[119-121] By examining the wellbeing of the family caregiver as a primary outcome, we will be able to detect how the demands and care needs of their loved ones are affected by the interventions. In addition, among family caregivers of people with AD, there are high rates of anxiety, stress, and depression.[122,123] Research has shown that poor caregiver mental health was associated with increased patient mortality, even after controlling for sex, age, dementia severity, and patient mental health.[124] Family caregivers experience anxiety when advocating for their loved ones health care needs.[125] NDR training may minimize anxiety. Thus, we will measure secondary outcomes of 1.) Anxiety (Patient-Reported Outcomes Measurement Information System (PROMIS) - Anxiety) and Neuro-QoL Caregiver-specific Anxiety [126] 2.) Caregiver Stress (Caregiver Stress Index), 3.) Caregiver Burden (Zarit Family Caregiver Burden Scale)[127] 4.) Fatigue (PROMIS)[128], 5.) Self-Efficacy as measured by PROMIS General Self-Efficacy and Caregiving Self-efficacy scales[129-131]and 6.) Received Support as measured by PROMIS Emotional/Informational Support, and Social Roles.

Table 3: Process and Patient-Centered Outcome Measures

Constructs	Measurement	Months		
		0	1	3
Patient Centered Outcomes				
Well-Being	**(Primary outcome)** Neuro-QOL – Positive Affect and Well-Being – Short Form	X	X	X
Anxiety	*PROMIS Ca Adult Item Bank Emotional distress–Anxiety; NEURO-QoL Caregiver Specific Anxiety	X	X	X
Satisfaction with Social Roles	PROMIS Ca Satisfaction with social roles/activities	X	X	X
Caregiver Burden	Zarit Family Caregiver Burden Scale	X	X	X
Fatigue	PROMIS Ca Fatigue	X	X	X
Self-Efficacy	PROMIS General Self-Efficacy – Short Form, Caregiving Self Efficacy	X	X	X
Received Support	PROMIS Emotional Support – Short Form, PROMIS Informational Support – Short Form, PROMIS Satisfaction with Social Roles/Activities	X	X	X
Intervention Specific Outcomes				
Feasibility	Study Recruitment Rates (count)	X	X	X
	Study Retention Rates (count)	X	X	X
	Acceptability (USE & SUS)	X		
	Completion of NDR Training Exercises	X		
Negotiation Processes/ Communication	Dutch Test for Conflict Handling (DUTCH)	X	X	X
	Knowledge of Negotiation Strategies (Survey)	X	X	X
	Utilization of Negotiation Strategies (Survey)		X	X
Program Assessment	Perception of the assigned intervention program, satisfaction, progress. Likert scale. Open-ended questions to obtain qualitative data on subjects' perception.	X	X	X

Qualitative Measures. In addition to the quantitative measures, we will ask qualitative interview questions immediately after the NDR training, and at 1 and 3 months. The open-ended question immediately after the training will ask about how the NDR training was perceived, means to improve, and any areas that were missing. At the 1- and 3-month intervals, the interview will ascertain the perceptions of family caregivers towards the NDR training, experiences with conflict or dispute resolution, and the utility or real-world use of the NDR training. Table 4 provides sample questions. These constitute a preliminary draft set of questions; we will work with our community partners to refine and finalize the items. Our team has extensive experience in health literacy and the development of easy-to-understand interviewer-administered surveys and protocols. Through these in-depth interviews we will explore the attitudes and beliefs of our participants regarding their knowledge, perceptions, and use of the NDR training intervention materials.

Table 4: Sample Questions for Qualitative Interviews

1. Have you experienced any conflicts pertaining to the care of your adult with AD? If so, can you please describe it?
2. Have you used the NDR training? If so, how? Please describe the situation. If not, why?
3. What aspects of the NDR training have been the most valuable? Least valuable? Surprising? Why?
4. How has NDR training affected your ability to handle conflicts?
5. Are there any other aspects of your life where you have used the NDR training? Please describe.

Data Collection. We will utilize REDCap Surveys software for data entry.[132] REDCap is a secure, encrypted, Web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data

entry; 2) audit trails for tracking data manipulation and export procedures; and 3) automated export procedures for seamless data downloads to common statistical packages. This software allows for straightforward electronic entry of responses and can generate output data files compatible with statistical programs. Drs. Lindquist and Kim will oversee the database structure and quality assurance activities.

Data Analysis: Power Calculation. The goal of this research is to inform a RCT trial of an optimized intervention. We will achieve that goal by evaluating feasibility and generating effect sizes of each component on changes in outcomes. The effect sizes will inform which components to retain in the optimized intervention and be used to power a subsequent trial. The pilot trial is not powered for hypothesis testing; however, a power calculation was run to determine the effect size this pilot trial will be powered to detect. With 120 subjects total and 40 subjects in each component group, we will be able to detect effect sizes of 0.65 with 80% power using a two-sided t-test at a type I error rate of 5%. For the primary outcome of Neuro-QOL Positive Affect and Well-Being, this equates to a mean difference of 3.9, assuming a standard deviation of 6. Calculations employed Rochon's GEE method, as implemented in SAS GEESIZE v. 3.1 macro implemented by Dahmen.[133-136]

Data Analyses: Aims 2 and 3 Quantitative. Data will be stored on a HIPAA-compliant server with secure access for approved study staff. Analyses will be conducted using SAS 9.4. For **Aim 2a**, we will calculate averages of acceptability ratings, number of exercises completed (retention to treatment), and prescribed strategies documented (compliance). These data will be used to derive expected usage rates for a future trial. For **Aim 2b**, we will assess the effect of each component on changes in Neuro-QOL – Positive Affect and Well-Being across time (baseline-1 month post-intervention), which will be done by comparing combinations of participants across conditions. Analyses will be conducted using intent-to-treat linear mixed effects models, accounting for data collected at multiple assessment time points nested within individual participants. For each component, we will test differences in change in outcomes across time, with baseline values as the reference. Thus, the effects will be modeled as component x time interactions. Cohen's *d* will be calculated by dividing the mixed effects model derived intervention effect estimate by the pooled standard deviation of the outcome. We will also report results disaggregated by sex and test sex as a moderator to evaluate sex differences in outcomes, which will inform the need for any sex-specific approaches in an optimized intervention. For **Aim 3**, exploratory analyses using linear mixed models will be performed to test two-way interactions between components on changes in weight and binge eating (e.g., Component 1 x Component 2 x time). Interaction tests are to determine if a set of components impact the overall effect and thus should be retained together in the optimized intervention.

Data Analysis: Aims 2 and 3 Qualitative. Responses from the open-ended questions in the electronic follow-up interviews will be uploaded into NVivo10 for analysis. Responses will be analyzed using constant comparative techniques,[137] led by Dr. Lindquist who has experience with qualitative data analysis. The coders will independently assess subject responses for focal themes, then convene to compare and compile findings, creating a preliminary list of categories and major themes.[138] Identified themes will be discussed and refined through a series of coder meetings, during which coders will triangulate their perspectives and resolve any identified discrepancies through discussion. The coders organized the content into themes relevant to participants' discussions of how the NDR training was utilized and what can be done to improve effectiveness for larger studies. ***Power.*** Based on previous research showing that 12 interviews are enough to reach thematic saturation in qualitative studies[139,140] and our own experience conducting qualitative studies, we anticipate reaching thematic saturation with the recruited number.

Minimization of Lost-to-Follow Up for assessment will be accomplished by continuing to follow up with patients even if they have completed or dropped out of treatment and compensating participants for completing assessments. Our methods have achieved more than 90% follow-up adherence for assessments. Subjects will be compensated for each survey completion.

Potential Challenges & Alternative Approaches. As with any trial, there is the chance that research activities extend beyond their expected timeline (e.g., challenges with design or recruitment). To avoid potential delays, we have planned a timeline like our prior PCORI-funded tool developments to design the intervention, so there is little risk of outright failure. Further, recruitment goals are conservative relative to the number of potential participants from three referral sites. One concern is that it is not clear how to separate out the potential outcome of NDR training on the well-being of the caregivers from the care-related stresses and strains in their daily lives. We will not be able to test this concern in the planned trial but will be able to collect additional information to inform and parse this out in future RCT trials examining efficacy.