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Palliative Care Needs of Children with Rare Diseases and their Families

IRB Approved Protocol Version 6

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PA17-018 SPECIFIC AIMS: Palliative Care Needs of Children with Rare Diseases and their Families.

In the United States (U.S.), a rare disease is defined as a particular condition affecting fewer than 200,000 persons.[1] Pediatric patients with rare diseases experience high mortality with 30% not living to see their 5th birthday.[2-4] For children with cancer and HIV, pediatric advance care planning (pACP) has proven to improve communication, spiritual and emotional well-being for the children and their families.[5-12] Pediatric ACP is a key component of pediatric palliative care,[13-16] which involves preparation and skill development to facilitate discussions about future medical care choices. In the U.S., family caregivers of children with rare disorders (hereafter referred to as families) are expected to provide a level of care that, until a few decades ago, was reserved for hospitals.[17] Due to the uncertainty of a life threatening diagnosis, heavy care demands, and factors such as social isolation, rare diseases can exact a severe emotional toll on families.[18,19] Families also share in common the likelihood that they will be asked to make complex end-of-life (EOL) decisions for their child. Children with ultra-rare disorders are a heterogeneous group often with co-morbidities, resulting in their exclusion from research,[20] thereby creating a health disparity for this vulnerable population. Available research on families of children with rare diseases lacks scientific rigor.[21-32] Although desperately needed, there are few empirically validated interventions[13,14] to address these issues.[33] Accordingly, there is an urgent need for pPCEOL interventions to ease the suffering of these families, a goal of pPCEOL.[34-39]

Therefore, the objectives of the proposed study are (1) to close a gap in our knowledge[40] by assessing families' needs for support in a heterogeneous group of children with serious, advanced, ultra-rare diseases with and without comorbidities, who are unable to participate in shared medical decision-making; and (2) to test one such pACP intervention which may empower families by providing some control in a low control situation and increase families' capacity to participate in EOL decision making. The *FAmily CEntered (FACE) pACP* intervention, proven successful with cancer and HIV,[5-12] is adapted to children with ultra-rare diseases. Theoretically[41-44] informed and developed by the PI, **Lyon**[5,7] and Consultant, **Briggs**,[5,7] the proposed intervention will incorporate *Respecting Choices Next Steps Pediatric ACP™ (RC)*, developed by **Briggs** (unpublished) and Hammes,[45] specifically tailored for families whose child is unable to participate in health care decision-making. Our consultation with families of children with rare diseases and the National Organization for Rare Disorders (NORD) revealed that basic pPCEOL needs should be addressed first, prior to a pACP intervention. For the study to be able to meet families where they are, prior to randomization, all families will complete the *Carer Support Needs Assessment Tool (CSNAT),*©[46-51] adapted for use in pediatrics in our preliminary research through collaboration with NORD and affected families. In The CSNAT Approach, facilitators assess the prioritized pPCEOL needs and developed Shared Actions Plans for decision-making support. We propose pilot testing the three weekly sessions of FACE-Rare: CSNAT *plus* Respecting Choices, using a rigorous intent-to-treat, single-blinded, randomized controlled trial (RCT) design with 30 family/child dyads with 3-month post-intervention assessments. We will accomplish the objectives of this application by addressing the following specific aims:

AIM 1. To evaluate the initial efficacy of FACE-Rare in a pilot RCT on <u>primary outcome:</u> family quality of life (QoL) at 3-months post-intervention, controlling for co-variates (age, sex/gender, race of family caregiver) to seek an effect size for a future R01.
Hypotheses (H) 1a: FACE-Rare families will report significantly better QoL (emotional, spiritual) compared to controls.
H1b: Family caregiving appraisals will moderate effect of FACE-Rare on QoL outcomes.
H2c: Religiousness will moderate the effect of FACE Rare on QoL outcomes.

AIM 2. To evaluate <u>process outcomes</u> with respect to <u>satisfaction</u> with study participation.
H 2: FACE-Rare families will report significantly greater satisfaction, compared to controls.

AIM 3. To evaluate the initial efficacy of FACE-Rare on <u>secondary outcomes:</u> plans and actions: completion of and documentation of advance care plans in the electronic health record at 3-months post-intervention.
H3a: FACE-Rare families will have a significant higher probability of completing pACP documents for their child, compared to controls; **H3b:** FACE-Rare families will have a significant higher probability of having pACP documents locatable in the electronic health record, compared to controls.

Exploratory AIM. To evaluate the initial efficacy of FACE-Rare on child healthcare utilization (hospitalization, surgeries, and ER visits etc.), compared to child healthcare utilization of control families. ***Hypothesis:*** *Caregiver-identified pPCEOL needs will differ significantly by gender, race and ethnicity, e.g. Blacks in the FACE-Rare (RC) intervention will complete advance care planning documents for their child at a rate comparable to non-Blacks, and at significantly greater rates compared to Controls.*

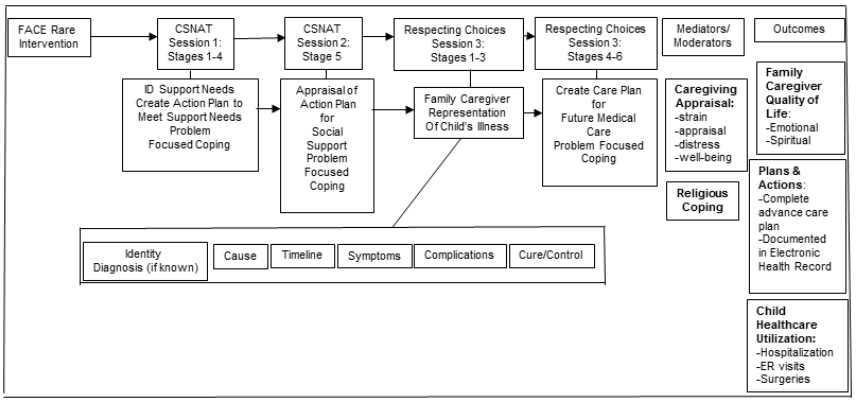
Our *long-term goal* with this project is to develop a model of structured pACP and to integrate patient-centered/family-supported health service delivery models nationally and internationally, as standard of care for children with rare diseases who are unable to participate in shared EOL decision-making.

A. Significance

A. Significance A.1. Pediatric Patient-Centered End-of-Life Care for Children with Rare Diseases and their Families. This is the first study of families of children with genetic and metabolic conditions, termed collectively as rare diseases, designed to intervene to support the well-being of family caregivers and create advance care plans for future medical decision making. Surveys show that families of children with rare diseases are adversely impacted by lack of easy access to peer and psychological support.[19,21-24,52] Only one intervention is described for families of children with rare diseases-a Swedish residential, competence program which increased active coping. However, this intervention did not address pACP, critical to palliative care.[15,39,53]

A.1.a Preliminary Studies. Efficacy of palliative care interventions involving pACP. Healthcare professionals may be reluctant to introduce pACP, believing families will not be comfortable talking about pACP.[54] However, in an RCT of FACE pACP conducted by **Lyon** and colleagues, families reported the experience to be worthwhile, although emotional.[55] FACE also increased families' understanding of their child's end-of-life treatment preferences, compared to controls;[56] and decreased HIV-specific symptoms through treatment congruence.[57] This effect was significantly moderated by religiousness.[57-60]

Figure 1. Transactional Stress & Coping Theory—Model of Family Caregiver Coping with Child's Rare Disease (Health Threat) through Problem Solving



Transactional stress and coping theory through problem solving (Figure 1) is the basis for our intervention.[61] This theory posits religious coping moderates health outcomes,[61-65] which is supported by rigorous research.[66-72] Religiousness and spirituality are different.[73-75] Previous FACE research demonstrated religiousness impacts QoL outcomes, in some cases decreasing spirituality and QoL.[76,77] Study findings may inform future interventions to address religious beliefs and practices associated with poorer QoL.[79,80] Rigorous adult clinical trials[81,82] demonstrate that interventions which promote active problem solving are more effective than other interventions in reducing caregiver burden, increasing caregivers' ability to cope, and improving their QoL. Both models (CSNAT and Respecting Choices) integrated into FACE-Rare promote active problem solving. The theoretical framework proposed here also integrates caregiver representation of illness[41,42,83] which posits an illness representation has five dimensions: identity, cause, time-line, consequences, and cure/control,[43] which the adapted Respecting Choices® intervention incorporates into their interview (**Appendix A**).[84] Respecting Choices decision-making tools are also sensitive to the disabilities community[85] important to our disabled study population. In keeping with community stakeholders advice,[41] palliative care needs will be assessed using the CSNAT *before* pACP. **Aoun (Co-Investigator)** demonstrated that the CSNAT model improved family caregivers of adults emotional QoL and identified needs and services that prevented medical crisis.[46-49,86] See **D.5.a** and **Appendix B** for details and the CSNAT tool. The proposed FACE-Rare intervention is consistent with parental perspectives for pACP[87] desiring a gradual approach,[88] which keeps all options open.[89] We will test the initial efficacy of FACE-Rare for improving families' caregiver appraisals, and QoL, consistent with NINR's mission to support research designed to maintain caregiver QoL.[90]

A.2. How pACP May Benefit Family Caregivers of Children with Rare Diseases A.2.a. Improved palliative care. The scientific premise of the proposed research, that family-centered pACP will improve families' QoL, stems from research with families of adult patients.[90-102] FACE-Rare is consistent with the NINR's *Conversations Matter® Campaign*[103] to increase awareness of and improve communication about palliative care. FACE-Rare may increase health equity in the use of palliative care by African-Americans[91,104]

by providing equitable access to and provision of pACP for African-American caregivers. Previous FACE trials significantly increased positive caregiving appraisals, compared to controls;[105] and decreased families' anxiety compared to controls.[106] Male family anxiety was significantly lower than females.[106] Little is known about sex differences in the impact of pACP on family caregivers. We will explore sex as a biological variable.

Acceptance of FACE among African-American families has been high.[6,9, 56] Among African-Americans living with HIV (n=192), 91% in the FACE intervention completed an advance directive, while only 15% in the control had completed an advance directive.[107] Study findings may increase equity in pACP, recognized by the Centers for Disease Control as minimizing suffering,[104] and improving public health.[108] Study outcomes are related to the National Consensus Project domains for palliative care:[109] psychological (emotional health, caregiver strain, caregiver distress), social (positive caregiving appraisals, family well-being), and spiritual (meaning/peace) and attend to the cultural and ethical domains of care.[110-113] There is an ethical imperative to engage in pACP, [114] despite the real concerns about the emotional impact,[56,115-117] because these conversations may actually support hope.[118-122] **A.2.b. Development, Feasibility & Beta Testing of Integrated 4-session FACE-Rare.** Our team developed and beta-tested the integrated FACE-Rare intervention at Children's National.[41] Of 9 families approached, 8 enrolled and 7 completed baseline. All 7 children had total parenteral nutrition (TPN) and 5 were wheelchair bound. All family caregivers were mothers and 43% African-American. Of the 6 mothers who began Session 1, 100% completed all 4 sessions and the 2-week follow-up assessment. The most frequently rated support need for their child, "Knowing what to expect in the future when caring for my child." Satisfaction ratings demonstrate 100% reported the sessions were useful and helpful, while half felt sad talking about goals of care. Two African-American fathers participated in creating advance care plans. This is significant as male caregivers are rarely studied.[123] They have agreed to participate in the Community Advisory Board to increase male caregiver participation in FACE-Rare. See **Letters of Support**. Average time to complete questionnaires was 27 minutes and families reported no respondent burden.[124] Findings demonstrate feasibility and acceptability. Families who participated in the development and beta-testing will not be eligible to participate in this R21. Parents reported, "Dealing with perpetual grief" and "Living on the precipice." Overall impact is high because findings will improve scientific knowledge of clinical practice supporting family caregivers whose children experience high rates of mortality[125change to Specific Aims number] and may decrease family caregiver strain, associated with higher overall mortality for family caregivers of older adults.[125]

B. Innovation B.1. Clinical Innovations. FACE-Rare offers (1) the opportunity to explore pACP, fora group not previously recognized in need of intervention; [126] (3) telemedicine to reach and follow-up families in ways not previously possible (see **Resources**); (4) a Community Advisory Board comprised of in part of fathers to increase male caregiver participation; (5) integration of caregiver illness representations,[42-44] with transactional stress and coping theory;[44,61] and (6) respect for individual differences.[127] Findings may guide standard-of-care evidence-based practice[128] to overcome critical barriers[129,130] to progress in palliative care for this "orphaned" group, meeting NIH's notice of interest addressing high-priority research in pediatric and end-of-life care.

B.2. Research Innovations. This R21 refines previous research by using a rigorous intent-to-treat, single blinded, prospective RCT pilot design that enables us to (1) evaluate the initial efficacy of FACE-Rare; (2) examine outcomes that are measurable and valid across sex/gender and ethno-cultural perspectives; and (3) prevent bias by assuring Assessors are blind to random assignment. This R21 is consistent with NINR/NIH's Science of Caregiving (2017) noting the importance of caregiving across the lifespan. If the aims are achieved, a future R01 will use advanced statistical methods[131-136] and be informed by statistical advice from rare disease investigators,[136] enabling us to track changes in goals of care over time, i.e."regoaling process."[137]

C. Investigators. We have assembled an international, interdisciplinary team which includes nurse scientists and early stage investigators with a history of collaboration. The PI, **Lyon**, is a clinical psychologist with unique expertise in palliative care behavioral interventions with families. **Fraser** is Director of the Myelin Disorders Program, a pediatrician, and an early stage investigator. **Fratantoni** is Medical Director of the Complex Care Clinic, a pediatrician, and early-stage investigator. **Hinds** is an internationally recognized palliative care pediatric nurse scientist. **Wang** contributes biostatistical expertise. **Ennis-Durstine** brings chaplaincy and ethics expertise. **Schellinger** is a nurse scientist from Respecting Choices. **Aoun**, a Public Health Demographer and Palliative Care implementation expert in Australia, brings research expertise using CSNAT. **Koenig,** a physician and nurse, brings expertise on the science of measuring/interpreting religious data.

D. Approach

D.1. Study Design. Investigators propose a pilot, two-arm, intent-to-treat, single-blinded, single-site, controlled RCT. Family/child dyads (N=30) will be enrolled and randomized to either the FACE-Rare intervention or treatment as usual (TAU) at a 1:1 ratio. The weekly 3-session FACE-Rare intervention of approximately 45-60

minutes each is comprised of the CSNAT approach [Sessions 1 & 2] *and* Respecting Choices [Session 3]. Investigators will test the initial efficacy of FACE-Rare on measurable outcomes at baseline and 3-months post-intervention. See **D5** for description of intervention. See **Power Analysis** for rational for 30 dyads.

D.2. Study Population. Nearly half of all pediatric inpatients in tertiary hospitals suffer from life-threatening diseases, and of these 82% have rare diseases.[139] A profile of children in the last year of life revealed that 56% had multiple complex chronic conditions.[139] For this reason investigators will include children with multiple-morbidities and include the large proportion of children with rare diseases treated in tertiary hospitals who are unable to communicate because of age, untreatable communication disorder, or intellectual disability. If multiple family caregivers participate, data will only be used for the primary caregiver, as determined by the couple. However, data will be collected from all participants for secondary analysis. *Child inclusion criteria* are (1) ≥1.0 years and <18.0 years at enrollment; (2) unable to participate in end-of-life care decision-making; (3) have a rare disease as operationally defined (See **Human Subjects**); (4) not under a Do Not Resuscitate Order or Allow a Natural Death Order; and (5) not in the Intensive Care Unit. *Family caregiver inclusion criteria* are: (1) ≥ 18.0 years at enrollment; (2) legal guardian of child and child's caregiver; (3) can speak and understand English; (4) not known to be developmentally delayed; and (5) not actively homicidal, suicidal or psychotic at the time of enrollment. Investigators will collect data on reasons for declining. **D.2.a. Study Site.** Children's National has an internationally recognized clinical genetics program, which records over 8,000 patient visits a year. The Children's National Rare Disease Institute is the first of its kind, focused exclusively on advancing the care of children with rare diseases. Eligible families will be enrolled from Children's National (N=32 dyads). Based on previous research,[5-9,56] investigators estimate 50% of families approached will agree to enroll, and 1% will be ineligible at secondary screening. So to achieve our randomization goal of 30 family/child dyads investigators will need to approach 32 families, which is realistic.

D.3. Recruitment and Retention Plan. Recruitment will use principles of inclusiveness. Investigators recognize that disease progression may impact enrollment and will take steps to accommodate caregivers. See **Human Subjects** and. Investigators will recruit during clinic visits, but not on day of diagnosis. The site's team is experienced and will use methods described by rare disease researchers.[4] Recruitment Procedures: Investigators will use a two-step recruitment procedure that ensures involvement of the primary provider or medical care team and reduces the potential burden to families. To minimize gatekeeper bias, prior to study initiation, investigators will conduct educational forums to discuss the study and address the legitimate reasons for providers to refuse approach. First, the study team will identify potential patients through review of future appointments. Second, the health care provider will confirm eligibility criteria, e.g. patient does have a rare diagnosis and the condition is not a result of prematurity, such as in pulmonary hypertension. The health care provider will let the study team know if there is a reason not to approach the family. Third, a trained member of the study team will approach the family by email and/or telephone, and/or text, as long as COVID-19 prevents face-to-face approaches. The selection, roles, responsibilities, and preparation of families are detailed in the **3-day Protocol Training.** "Because of COVID-19 and the difficulty with face-to-face recruitment posed by the epidemic, we are requesting to ADD to our recruitment strategy a modified form of Snowball Recruitment. 1. Potential participants will be contacted by previous participants (from the beta testing phase of our study in 2019) who are currently members of our Community Advisory Board (CAB). We are asking them to tell other people about the study. The CAB member will use the IRB approved flyer to describe the study to other people (family caregivers of children with rare diseases, whose child receives care at Children's National, and whose child is between the ages of 1 up to age 18) who may be eligible. If interested these people will contact the researcher directly using the researchers' contact information on the IRB approved Flyer. This approach will protect patient privacy. 2. We will not be doing "cold calling." 3. CAB members will not be receiving any compensation for providing referrals or be offered incentives to provide referrals. 4. Current participants will not be required to refer others or incur any penalty for not referring other participants. 5. The CAB member do not have power over the potential participants, such as an employer-employee relationship, but may be members of various advocacy groups that support family caregivers." Consent and Enrollment: Family caregivers will undergo written informed consent using IRB-approved documents prior to participation in any study procedures or data collection. Investigators have IRB approval for a waiver of assent for the children, as one eligibility criterion is "unable to participate in healthcare decision making." Randomization and Blindness**:** Randomization will be triggered by computer following completion of the baseline assessment in the already established REDCap database. Employing an intent-to-treat paradigm, dyads will be randomly assigned to FACE-Rare vs. TAU at a ratio of 1:1. The FACE-Rare

facilitator will notify intervention or control families the day of random assignment and schedule the approximately weekly study visits for those randomized to FACE-Rare and assessments for those randomized to control. Allocation will be concealed from the Assessor to prevent bias during the administration of outcome questionnaires, process measures, and chart abstraction. **D.4. Retention and Attrition.** Investigators will use proven procedures for retention.[4] Investigators have a +/- one-month window for completion of 3-month post-intervention assessments to meet family needs. Using such procedures, only 5%[9]-7%[6] attrition was documented from earlier trials at 3-months post-intervention.[56,57] Use of TAU in FACE-TC trials did not result in significant differential attrition over time by study arm.[6,106] Weekly staff meetings will identify retention problems early. Monthly conference calls with investigators and the Community Advisory Board will rectify them. Telemedicine should mitigate transportation/child-care/immune compromise barriers (e.g. avoid hospital during flu season). Thus, investigators conservatively estimate 15% attrition.

D.5. Intervention FACE-Rare: [The CSNAT Approach Paediatric Sessions 1 & 2 *plus* Respecting Choices® Next Steps ACP Session 3] or **TAU Control.** Both arms will receive palliative care information at enrollment.

D.5.a CSNAT: CSNAT is an, evidence-based, person-centered process of family caregiver assessment and support in palliative care.[46-51] It is a caregiver-led, practitioner-facilitated approach to decreasing caregiver burden, tested in RCTs with adults[46-51] and adapted during the preliminary study for pediatrics.[41] The CSNAT pediatric, adapted during the development phase,[41] adopts a screening format structured around 16 broad support domains, described in Figure 2. Each domain represents a core family caregiver support domain, falling into two distinct groupings: those that enable the caregiver to care; and those that enable more informal direct support for caregivers. Four response options indicate the extent of support requirements, from 'no more' to 'very much more.' *The CSNAT approach* has five stages: (**Session 1**) Stage (S) 1: The CSNAT tool is introduced to the family caregiver by the facilitator. S2: The family is given time to consider in which domains they require more support. S3: An assessment conversation takes place wherein the facilitator and family discuss the domains for which more support and their priorities. S4: A shared support plan is made in which the family caregiver identifies the type of input they would find helpful. In (**Session 2**) S5: A shared review with the facilitator is conducted of what the family has operationalized during that time

Table 1	Session 3- Next Steps: Respecting Choices pACP®
Found-ation	RC pACP for children with life-limiting illnesses and unable to participate in healthcare decision-making
Goals	To facilitate conversations with the family-6 about their child's medical condition, fears, values and beliefs (including religious and spiritual) and hopes (including hopes if initial hopes are not realized).To prepare the family for future medical decisions if the worst were to happen.
Process	**Stage 1** assess family's understanding of child's illness: hopes, fears, concept of living well; **S2** explore family's experiences with child's hospitalization; **S3** review goals of care and set the stage for future healthcare decisions. **S4** Explore goals for future healthcare, using a situation-based Advance Care Plan document; **S5** Questions for child's provider identified and written on post-card; **S6**: Follow-up Plan.

D.6.a. Next Steps: Respecting Choices (Session 3): Respecting Choices pACP conversation engages families in a process for how to make future medical decisions consistent with their goals and values. See Table 1 for content. This session is audio/videotaped for fidelity purposes.

D.5.b. Treatment as Usual Control (TAU): To minimize the burden to families, we have chosen a TAU comparison condition. Current practice for minors with life-limiting illnesses is to defer initiation of pACP discussions until a medical crisis.[139]

D.6. Data collection procedures & contamination. Assessments occur at baseline and 3-months post-intervention with brief process/satisfaction assessments at Study Visits 2,3,4. This interval replicates earlier trials and is feasible within the 2 year R21 mechanism. The assessments and intervention will be administered by a research team comprised of: Blinded RA-Assessor, trained CSNAT-Interventionist, and certified Respecting Choices-Interventionist. Participation in the FACE-Rare study may cause physicians or families to initiate pACP conversations and document completion in the electronic health record, thereby creating contamination. Children's National has an established palliative care program and policies supporting pACP. Control families will not be denied these services. Control Families will be offered the intervention after completion of their study activities. However, evidence from our previous FACE trials demonstrated the FACE effect size is large enough to mitigate any contamination that may occur,[6,9,56,57,107] For example, an effect size of 0.84 vs. 0.029, corresponding to an odds ratio of 176. Similarly, despite palliative care consultations with goals of care discussions, research indicates palliative care teams rarely complete ACPs.[140-142] **D.6.a. Study visit protocol. (Figure 2).** *Screening Visit:* Following procedure described in **D.3**, the RA presents the initially eligible family with the IRB approved Information Sheet. If the family is interested, after consent and waiver of

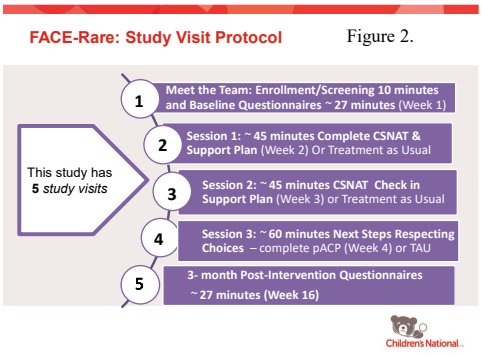


Figure 2.

assent, the RA will conduct further screening for inclusion/exclusion criteria. *Baseline Visit:* At enrollment and prior to randomization, baseline measures in Table 3 will be obtained. Attendance will be recorded to assess effects of full vs. partial participation in FACE-Rare. *Follow-up Visit:* Blinded Assessor will obtain follow-up measures from families at 3-months post- intervention in person (clinic or home visit), by telephone or Telemedicine. See **Resources on Telemedicine**. **D.6.b. Measures.** Measures (**Table 2**) will be administered to the family by the blinded RA-Assessor. Investigators selected well-established measures with good reliability, validity, and normative data to increase replicability. Chart abstraction will be conducted by the blinded Assessor. A second blinded researcher will provide a validity *and* reliability check. Interrater reliability testing will be conducted. Rate differences will be reconciled by consensus, following well established procedures.[14,145] Disagreements will be resolved by the PI. See **Project Narrative** for questionnaire details.

Table 2: Measures	**Method**	**Time**	**Description**
Primary Outcomes: *BL=Baseline *mo=month			
Beck Anxiety Inventory[143]	Survey	BL, 3 mo	**QoL:** emotional health. 21 items. Total Score will be used in analysis.
FACIT-Spirituality-EX-Vs-4)[144]	Survey	BL, 3 mo	**QoL**: spiritual (meaning/purpose, peace). Is culturally sensitive to those with non-theistic beliefs. 23-items. Total Score will be used in analysis.
Advance Care Document for Children with Rare Diseases[84]	Survey	3 mo	**ACP Documentation in EHR & Decisional preferences**- to continue all treatments; to continue all treatments with exceptions noted; to stop all treatments but comfort care.
Standardized Data Abstraction Operationally defined[14,45,145,146]	*Chart Abstract*	*BL,3 mo or close-out*	**Child healthcare utilization**: initiation of palliative care consultations, # of days in palliative care prior to death, hospitalizations, Emergency Department visits, intensive care unit use, surgeries, place of death.
Moderators:			
Brief-Multidimensional Measure of Religion and Spirituality[62,63]	Survey	BL, 3 mo	**Religious Coping**: 5 items from our previous research: attend religious services, feel God's presence, pray privately, identify as religious, identify as spiritutal.[12,57,58]
Family Appraisal of Caregiving Questionnaire[147]	Survey	BL, 3 mo	**Caregiver appraisal**: caregiver strain, positive caregiving appraisals, caregiver distress, family well-being in past two weeks. 25 items.
Time-Invariant Covariates:			
Demographic Questionnaire	Survey	BL	Age, sex/gender, race, ethnicity of family caregiver and child. Child technology dependent. Education, household income, marital status, employment.
Process Measures:			
Satisfaction Questionnaire[7,56]	Survey	Visit 4	Study specific process measure to assess adverse events and benefit/burden of participation. 12 items.
Quality of Communication Questionnaire[182]	Survey	Visit 4	Study specific process measure to assess how participating families perceived the interviewer's quality of communication and rate the overall quality of discussion. 5 items. Adapted from Curtis et al.[182]
Role stress[148]	Survey	Visits BL, 3 mo	Visual analogue scale 0-100. "How stressful is it for you to make medical decisions for your child?" 1 item.

including scientific and clinical leadership. **Lyon** will also have primary responsibility for practical issues in training and implementation. **Thompkins,** will provide oversight of logistics necessary to conduct the study, regulatory oversight, data collection, and management. Children's National is the data coordinating center. See **Overall Structure of Study Team. D.7.a. Site Initiation.** To begin screening/enrollment (1) all personnel are certified in Human Subjects Research training; (2) personnel are recruited and trained for their roles. **Lyon** and **Thompkins** will verify all components in place for the logistics of screening, enrolling, scheduling, performing assessments, administering interventions, and collecting the data. Training and competency criteria will be used to ensure fidelity to the protocol. A manual of operating procedures will be created. **D.7.b. Communication.** The PI is responsible for facilitating all communications and will meet weekly, face-to-face, with the research team (RA-Interventionist, RA-Assessor, **Thompkins**). Monthly conference calls will be had with PI, Co-Is, and consultants. **Lyon** and **Schellinger** will supervise Respecting Choices Facilitator monthly through conference calls. Identified barriers will be addressed and appropriate action taken. Meeting minutes/benchmarks will be kept by **Thompkins** and circulated.

D.8. Monitoring of Trial Conduct will be ongoing. **D.8.a. Intervention Fidelity**. Fidelity to CSNAT competency criteria will be accomplished during **3-day Protocol Training** and monitoring by **Lyon** in consultation with **Aoun**. **Lyon** and **Schellinger** will review all recordings of Session 3, Respecting Choices conversation to ensure intervention fidelity. **D.8.b. Procedure Monitoring. Lyon** and **Thompkins** will monitor ongoing IRB compliance, documentation and preparation for annual continuing reviews. **Lyon** and/or **Thompkins** will assure standardization of procedures, resolve any problems that are identified, confirm that all consents have occurred properly, and maintain participant and regulatory data **D.8.c. Data quality monitoring.** The REDCap database from previous FACE studies has been updated and expanded for this study. The system in place for data entry and implementation will be updated. See **Resources** for details. **D.8.d. Safety Monitoring Committee (SMC)** will meet twice yearly or more often as needed. See **Data Safety and Monitoring Plan.** The external SMC will be assembled by **Lyon** and have the responsibility of reviewing safety information, study progress, and other relevant data. Duties will include review of any serious adverse event (SAE) or adverse event (AE), recommending follow-up or further action to the PI.

D.9. Analytic Plan. Various statistical methods, such as descriptive statistics, paired t-test, reliable change index (RCI), Fisher's exact test, and generalized estimating equation (GEE) models will be used to evaluate the proposed aims. All models will be estimated Bayesian approach.[149-151] As such, data non-normality due to the small sample size can be handled in modeling under the assumption of missing at random (MAR). MAR is a plausible assumption that allows missingness to be dependent on observed measures (e.g., individual characteristics, intervention assignment, and/or baseline outcome measures).

AIM 1. *To evaluate the initial efficacy of FACE-Rare in a pilot RCT on primary outcome: family QoL at 3-months post-intervention to seek effect sizes for a future fully powered R01*. **Hypotheses (H) 1a:** FACE-Rare families will report significantly better QoL (emotional, spiritual) compared to controls. We will first describe the level of the outcome measures at both baseline and 3-month post-intervention by intervention group. Each group's pre- and post-intervention outcome levels at will be compared using paired t-test, respectively. Difference in change of each QoL measure from T_1 to T_2 between intervention groups will be examined using t-test. We will then apply the reliable change index (RCI)[152,153] to assess how many individual patients in each intervention group would make a clinically significant amount of improvement in each of the QoL measures based on their RCI scores. The bias in outcome changes caused by measurement errors in the QoL scores will be taken into account in RCI. We will provide graphic portrayal of individual outcome changes and RCIs by intervention group. An RCI of ±1.96 will serve as criteria for classifying the patients into categories of improved, unimproved, and deteriorated based on their QoL scores and RCIs. Those categories will be compared by intervention groups using two-sided Fisher's exact test. Based on our previous studies, we will assume a reliability of 0.80 for each of the QoL measure for conducting RCI. Because the focus on the individual rather than the group as a whole, data provided by the RCI allows the identification of individuals whose QoL measures have only changed marginally, or in an unusual direction, allowing the identification of subgroups for further analysis. The RCI thus also provides a systematic screening tool that has some advantages over the traditional visual inspection or setting cut-off points for inclusion based only on change relative to the group.

Finally, we will use GEE model to examine the intervention effect on QoL, controlling for covariates (due to the small sample size, only a few covariates-- age, gender, and race-- will be included). Bayesian approach that has superior performance in small samples without reliance on asymptotic and data normality assumptions will be used for model estimation. The goodness of fit of the model will be assessed by the posterior predictive checking.[154] If model fits data well, the 95% confidence interval of the difference between the observed and replicated model χ^2 values should center around zero, and the posterior predictive p-value (PPP) should be greater than 0.05.[151,154] Statistical inferences will be made by examining the range of parameter estimates that captures 95% of the posterior probability distribution (i.e., 95% Bayesian credibility interval, CI). If the 95% CI of a slope coefficient estimate does not cover zero, then the coefficient is statistically significant at α=0.05 level.[150,154,155] All models will be implemented using Mplus 8.3.[156] The effect size of FACE-Rare intervention with respect to each specific outcome measure that will be used for our future R01 application will be estimated by the standardized outcome mean difference between intervention groups. The standardized slope coefficient of the intervention variable in a GEE model is the estimate of effect size, net of covariates.

H1b. *Family caregiving appraisals will moderate effect of FACE-Rare on QoL outcomes*. The interaction between a caregiving appraisal variable and intervention will be included in the GEE model described above to examine whether and how the intervention effect on QoL measures would be moderated by the family caregiving appraisal. If the interaction is statistically significant, we would conclude the intervention effect on the outcome depends upon the value of the caregiving appraisal. A positive coefficient (e.g., 0.2) of the interaction indicates that intervention effect would increase the magnitude of this coefficient (e.g., 0.2), corresponding to one unit increase in the caregiving appraisal score. Each appraisal measure will be recoded as the deviation from its grand mean so that the recoded appraisal measure has a meaningful 0 that represents the mean level of the appraisal in the sample. As such, the main effect of intervention is interpreted as the intervention effect corresponding to the mean level of the original appraisal measure (i.e., the 0 of the recoded appraisal measure). When the interaction effect is statistically significant, the corresponding main effect, no matter it is statistically significant or not, must remain in the model and be included in calculation of intervention effect.[157,158]

Testing H1c. Religiousness will moderate the effect of FACE Rare on QoL outcomes. The same analytical approaches proposed for testing H1b will be applied to test **H1c**.

AIM 2. *To evaluate the effect of FACE-Rare on satisfaction with study participation*.

H2: FACE-Rare families will report significantly greater satisfaction, compared to controls. The same analytical approaches proposed for testing **H1a** will be applied to test **H2**.

AIM 3. *To evaluate the initial efficacy of FACE-Rare on secondary outcomes: plans and actions: completion of and documentation of advance care plans in the electronic health record at 3-months post-intervention.*

H3a: *FACE-Rare families will have a significant higher probability of completing pediatric Advance Care Planning (pACP) documents for their child, compared to controls*. Difference in the odds of completing pACP documents at 3-months post-intervention between intervention groups will be first examined using two-sided Fisher's exact test and then exact logistic regression)[159,160] will be applied to examine the intervention effect on the odds of completing pACP, controlling for covariates (age, gender, race). **H3b:** *FACE-Rare families will have a significant higher probability of having pACP documents locatable in the electronic health record, compared to controls.* The analytical approaches proposed for testing **H3a** will be applied for testing **H3b**. **Exploratory AIM**. *To evaluate the initial efficacy of FACE-Rare on child healthcare utilization (hospitalization, surgeries, and ER visits etc.), compared to controls.* Previous studies suggest few cases in this brief time period, so descriptive statistics by intervention group without test will be reported with future plans to estimate costs associated with pACP. **Power & Sample Size Consideration.** Based on previous FACE research, [5,8,56] a sample size of 30 dyads will be sufficient to find statistically and clinically meaningful differences at 3 months-post intervention and provide an effect size for a future R01. With attrition at 15%, 25-26 dyads will be available at 3-months post-intervention. With a small sample, the quality of the standard errors, parameter coverage, the power of detecting effects, and the quality of overall tests of fit may be in question. However, parameter estimates are often dependable even through sample size is small. Having realized the small sample size, we have proposed Fisher's exact tests, exact logistic regression, and particularly Bayesian for statistical tests and modeling. As such, the proposed study would provide useful information about the effect size that will be used to power a future R01. Investigators may not have sufficient power to report sex differences for caregivers. However, we will report our findings separately by sex in progress reports and publications.
D.10. Brief Timeline. Investigators received IRB approval and completed the initial REDCap data base. Months 0-3: hire, train & certify project staff. Months 4-23: Ongoing recruitment, enrollment, assessments/data collection, fidelity monitoring, data cleaning. Months 23-24: Analysis and dissemination. See **Study Timeline.**
D.11. Alternative Strategies We will only study staff willing to work flexible hours and to inconvenience themselves to meet families' scheduling needs. Weekly meetings will allow for early trouble shooting. If under-enrolled, investigators will use CTSI-CN Power Trials to identify additional eligible children/families and/or add a study site. We will actively recruit fathers/male caregivers. See **Recruitment and Retention Plan**.
Future Plans: If R21 aims are achieved, a future multi-site R01 will test the full theoretical model to improve pACP for children with rare diseases and their caregivers through family engaged pACP.[161]

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK

1. Risks to Human Subjects

a. Human Subjects Involvement, Characteristics and Design

We will be studying family caregivers/legal guardians of children ages ≥1 to <18 years with rare diseases who are unable to participate in health care decision making; and retrieving protected health information on the children from the electronic health record (EHR). No data will be collected directly from the children, but PHI will be collected from the EHR.

Children's National Health System serves approximately 2,189 children who meet eligibility criteria, including children with Leukodystrophies; Intestinal Failure/Short Bowel Syndrome/Liver failure; Pediatric Cardiomyopathies; Organic Acidemias; Renal Failure in need of Renal Replacement Therapy (Dialysis and kidney transplants); Rare clotting disorders; Hemophilia A inhibitor, Severe. Our site has a history of successful research.

We will recruit for approximately twelve months until we enroll *30* family caregiver/child dyads who after completion of the baseline questionnaires will be randomized at a ratio of 1:1 into either the 3-session FACE-Rare Intervention Group (n=15 dyads) or Treatment as Usual Control Group (n = 15 dyads) with the goal of obtaining data from conservatively 21 dyads at 3 month post-intervention for statistical analysis. We have not had differential attrition in our earlier studies, as discussed in

Research Strategy. We estimate that approximately 43% of the sample will be African-American. To achieve our enrollment goal of 30 families, we estimate based on our previous studies that we will need to approach 62 families, which should be easily accomplished with the potentially available study population. Post-intervention questionnaires to asses study outcomes will be administered at 3-months post-intervention.

The current R21 proposal has received approval from Children's National's IRB, the IRB. The participant eligibility criteria have been developed with careful consideration to ensure the safety of the study participants.

Participant Eligibility Criteria

Child Inclusion Criteria:

- Diagnosed with a rare disease;
- Ages ≥1 year ≤18 years; *no infants under the age of 1 year are included;**
- Not in foster care;
- Unable to participate in health care decision making, e.g. due to developmental delay (IQ <70), neuromuscular disorder with no communication device, under age 7;
- Waiver of assent from the legal guardian;
- Consent from legal guardian;
- Primary diagnosis is not autism, cancer, cystic fibrosis, Down's syndrome, HIV, Duchenne's muscular dystrophy, sickle cell disease as a primary diagnosis. These conditions can be secondary to the primary rare disease. (Rare pediatric cancers are excluded from this announcement. The other disorders listed have disease specific studies available with respect to palliative care needs—one purpose of this proposal is to study those children and their families who have rare diseased that have been excluded from condition-specific research or have small studies of low quality);
- Not in the Intensive Care Unit;
- Not have a current Do Not Resuscitate Order or Allow a Natural Death Order.

*Infants are excluded as they are outside the scope of this Program Announcement (Communication with Project Officer). Children who already have an advance care planning guide are eligible: 1) to update; and 2) to be sure there was a conversation about goals of care and not just the form completed.

Inclusion Criteria for Family Caregivers/Legal Guardians of Children with Rare Diseases Ages

- Legal guardian and family caregiver of child with rare disease as defined above;
- Age 18 years or older; (We have excluded younger caregivers, because this may involve child protection issues which are beyond the scope of this project)
- Ability to speak and understand English;*
- Absence of active homicidality, suicidality, or psychosis determined at baseline screening by trained research assistant (RA);**
- Not known to be developmentally delayed;
- Consent to participate;
- Consent for his/her child to participate;
- Signed waiver of assent for their child.

*The requirement for understanding of spoken English is necessary for an appropriate level of participation and because they will be signing an advance care planning document that can be put in their child's EHR. Also, CSNAT has not been validated with non-English speaking participants. We

are currently running a small American Cancer Society funded trial to have our materials adapted for Spanish speaking family caregivers and adolescents with cancer.

**Family caregivers are less likely to be competent to participate in shared decision-making for their child if they are actively suicidal, homicidal or psychotic. Family caregivers who are suicidal, homicidal or psychotic at secondary screening will be referred for further assessment, treatment and not enrolled. If the legal guardian/family caregiver receives treatment and their symptoms are resolved, the dyad will be enrolled and randomized. Participants who are interested in the study but are "not ready" to participate will be followed and contacted regularly on a schedule they prefer, with their consent. They will be randomly assigned if and when the family caregiver becomes ready to participate.

Because of its sensitive nature and the use of advance care planning documents placed in the EHR, children who are in foster care and their family caregivers will not be recruited to participate in this study. Study personnel are experienced in providing accommodations for illiterate parents and family members, and these accommodations will be provided, including reading questionnaires to all family caregivers.

b. **Sources of Research Materials**, **Potential Risks, and Study Procedures**

Data collection will be confidential unless specifically required to be disclosed by state or federal law. Participants are assigned unique identification numbers used on all case report forms. Only Children's National will have information linking subject's personally identifiable information to the study ID number. Children's National maintain all study files and documentation in a secure area where access is limited to study personnel. Participants will not be personally identified in any publication that may come from this project.

There will be a Data Sharing Plan implemented at the end of the trial. See **Resource Sharing Plan**.

Research data will be gathered either by direct entry into the web-based database REDCap (see Methods) via protocol specific electronic forms, or, if the internet is not available, onto paper forms and later entered into the web-based database by RA-Assessors. Data on children will be collected from medical record review.

In addition, if family consent is provided, Session 3 will be recorded by videotape or audiotape (family preference) and reviewed by the PI, Dr. Lyon and Thompkins, for implementation of quality control with regard to fidelity to the protocol, avoiding contamination of the control condition and monitoring for safety. Families who decline to be audiotaped or recorded by camcorder will still be included in the study, but their data will not be available for fidelity check. In our previous studies approximately 10% of participants declined to be audio or video taped.

This proposed project has chosen to utilize face-to-face data collection over audio computer-assisted self-interviews (ACSI). The rationale for this choice of data collection was based on sensitivity of the interview content, caregiver preference based on our pilot studies of families of children with rare diseases and feedback from the National Organization of Rare Diseases (NORD), and the potential for an improved risk assessment.

a. Topic sensitivity: Due to the sensitivity of the topics discussed during the study interviews, we felt face-to-face conduct was preferable to ensure social respect to the study participants.
b. Participant perception: Participants from our previous studies relayed a positive experience from the face-to-face assessments and interviews and viewed it as a caring experience, versus an impersonal means of data collection.

c. Improved risk assessment: This technique will provide an additional way to protect the patients by providing study staff with the opportunity to directly observe emotional distress, or any additional risks, by using our standardized procedures described under **Adequacy of Protection Against Risks.**
d. Increased engagement: This approach increased engagement with staff which in turn enhanced retention of participants in our previous studies.

We will defer the study visit if privacy cannot be maintained, unless participants agree to the study visit, despite the presence of other patients/family members. We will code for this in our data.

Potential Risks to Subjects

Potential risks associated with the study interviews include:
1) Emotional distress or family conflict related to discussion the death or dying of one's child.
2) Disagreements may emerge regarding palliative care and goals of care decision-making specifically related to end-of-life treatment preferences. A primary purpose of this study is to contain the strong feelings that conversations about pACP may elicit and to use transactional stress and coping theory to problem solve any differences through the FACE-Rare Intervention. In the experimental group, the likelihood that care is in accord with families' preferences is higher than in the "usual care" condition and this is one of the reasons for conducting this study.
3) Conflict may emerge between family caregivers when there is more than one participating. These families will receive a referral to their respective ethics committees, which are comprised of experts in helping families talk through the risks and benefits of different treatment choices and experts in conflict resolution related to differing family values about end-of-life care. If the conflict is of a religious nature, the family will be referred to the respective chaplaincy program whose chaplains have expertise in this area as well.
4) A risk common to all research studies is breach of patient confidentiality.
5) There are no physical risks associated with the study procedures.

Recruitment and Retention Strategies

Recruitment will use principles of inclusiveness. See **Retention Plan** for more details. We recognize that disease progression may impact enrollment and will take steps to accommodate caregivers. Because research suggests early assessment of palliative care needs prevents future crisis,[48] we will recruit during clinic or other research visits, but not on day of diagnosis, nor will we recruit any family whose child is in the Intensive Care Unit. Each site's interdisciplinary teams are experienced in successful recruitment and retention of research subjects.

Recruitment Procedures: We will utilize *a three-step* recruitment procedure that ensures involvement of the health care provider or medical care team to reduce the potential burden to families. To minimize gatekeeper bias, prior to study initiation, we will conduct primary care provider and healthcare team educational forums to discuss the study and address the legitimate reasons for providers to refuse approach. The study team at each site will identify potential patients through review of future appointments. First, the study team will identify potential patients through review of future appointments. Second, the health care provider will confirm eligibility criteria, e.g. patient does have a rare diagnosis and the condition is not a result of prematurity, such as in pulmonary hypertension. The health care provider will let the study team know if there is a reason not to approach the family. Third, a trained member of the study team will approach the family by email and/or telephone, and/or text, as long as COVID-19 prevents face-to-face approaches. . Eligible families will be approached until 30 eligible dyads are enrolled. The selection, roles, responsibilities, and preparation of families are detailed in the 3-day Facilitator Training outlined. Dr. Lyon and colleagues are currently collaborating on a study that uses a similar procedure and have found it to be successful, i.e. not burdensome to the family caregiver.

Children's National has a history of success in recruiting children and families for participation in research studies. Currently, Children's National is running two clinical trials. We are especially sensitive to the distress of families of children living with rare diseases and to recruitment during the end-of-life. For this reason we will maintain the involvement of a Community Advisory Board of Families of Children with Rare Diseases and NORD throughout the study. See **Overall Structure of Study Team**. We will generate a list of potentially eligible participants and follow the procedures described in **Recruitment and Enrollment Plan.**

Attrition: See **Approach** for data on attrition. In the PI's judgment, Children's National has such low attrition because patients form strong attachment bonds with the clinical and research staff, a "positive institutional transference" (David Reiss, M.D. personal communication, former director of the Family Research Center at George Washington University).

Privacy: Part of our success in recruitment and retention is due to our staff members who are trained to be sensitive to the specific needs of families, particularly privacy and their rights as a research participant. At the time of enrollment, participants complete a "Contact Information Sheet." It asks: If I call your home, what kind of message is o.k. to leave? What is your preferred way for the research staff to contact you? Is it o.k. to send you something by email? Is there anything else you would like us to know when contacting you? This process establishes rapport and builds trust.

Not all patients will be in private rooms. Care will be taken to assure privacy during any bedside interviews. Moving from the hospital room to a private area will be done, if possible. Attempts will be made to conduct the study when participant is alone. The same procedures will be used for home visits. For families who are interested and to decrease participant burden, study visits can be conducted via Telemedicine. We will only use HIPPA protected systems. See **Resources**. Again, attempts will be made to conduct the study when the participant is in a private area.

Some families may give us permission to use their audio or videotapes for teaching purposes and for data dissemination. They will be asked to sign appropriate site-specific releases, consistent with the hospital policy of the site. These DVDs and videos will assist with future training, education and dissemination, sensitive to the privacy issues involved.

Confidentiality: Patient confidentiality will be appropriately protected in the process of data collection and storage. The protocol operational team will minimize the likelihood of breach of confidentiality by minimizing collected Public Health Information (PHI) and using randomly generated identification numbers. Questionnaires will contain only a study-specific ID number and no other identifying information. Patients will be identified only by study ID number, visit type and date. All documents and information pertaining to the study will be kept confidential in accordance with all applicable federal, state, local laws and regulations. Research data and participant records collected in connection with this project will be held in confidence unless specifically required to be disclosed by state or federal law. Participants will not be personally identified in any publication of the data from this project. For those child participants where only a handful of children worldwide have their genetic disorder, diagnosis will not be reported in study publications or professional presentations without the explicit, signed permission of the legal guardian(s), as the child's identity could be revealed. Rare disease journals have procedures for taking this into account as well. Any source documents that contain PHI (e.g., advance directive documents), will be kept in a secure location only accessible to study staff. These source documents will not contain the PID, only the signature of the parent/legal guardian. With the participant's permission, source documents will be entered into the child's medical record and given to the child's primary health care provider.

The project office is a locked room to which only study personnel have access. Original data are stored in locked file cabinets. Keys are tracked through a centralized system. Study personnel are

trained in the ethics of protecting confidentiality through course work, in discussion with the PI, and by completing the NIH course on protecting human subjects. Study personnel are trained to ensure compliance with HIPAA regulations protecting patient health information.

Appointments are scheduled to accommodate the needs of patients. Research Assistants (RA) availability will average 12 hours a day, and flexibility in availability to families is a key qualification for the job. RAs are selected, in part, based on the flexibility of their schedules, so that appointments can be made at times most convenient for families, including early mornings, evenings and Saturdays.

The Information Sheet scripts the way in which the study will be described to the patient. During training, study staff role play how to approach families. Enrollment/screening/baseline surveys will happen during the same visit, unless the family prefers otherwise. Three sources of contact information will be obtained from each dyad. This process averaged 27 minutes during beta-testing, as we always take the time to assess readiness and potential obstacles to completion of the study. Study staff will describe participant requirements, including time commitment and study documents to be completed. Study staff will also describe compensation for time. Once recruited and enrolled, legal guardians/families will receive reminder calls, postcards, birthday cards, and appropriate holiday cards from study staff.

The consent process describes the study in great detail. Our research experience is that the consent process is the best time to assess readiness to participate, enhance motivation, and eliminate individual or family barriers to participation. If there are two legal guardians, we will encourage both to enroll in the study. These choices create a number of dilemmas, addressed below.

Study Procedures for Legal Guardians/Family Caregivers

There are important concerns about selecting a family member to participate in advance care planning. We understand that the process of decision-making might be changed by having either one or both guardians present, and may also vary as a function of the gender of the guardian. The guardian most comfortable with discussing advance care planning may not be the same person who has the power to make important decisions in the family. For these reasons, we will invite and encourage both guardians to participate in Session 3 (Respecting Choices Interview and completion of Advance Care Plan), as this is consistent with clinical practice. Nevertheless, in our previous advance care planning studies, the majority of the surrogate-decision makers were biological mothers and less than 10% involved more than one family caregiver. However, in our beta-testing of FACE-Rare one-third of the female family caregivers did bring their spouse and their child with them to participate in Sessions 3 & 4, and in one case just Session 4. These sessions were completed face-to-face. When it came time to discuss the Advance Care Plan, one father very sensitively requested that the wheelchair bound and intellectually delayed child be placed just outside the room, where we could see her, so his daughter would not hear us talking about her advance care plan. Deep appreciation was expressed by the fathers for including the entire family. We will make every effort to accommodate the entire family whenever possible during the course of the study and examine study outcomes by sex of the family caregiver.

Resolving Disagreements

We are taking a very cautious approach and want to note that the issues to be addressed next <u>did not</u> arise during our previous studies. Nevertheless, we recognize the potentially charged nature of the study. In our preliminary studies the intervention proved sufficient to resolve differences about end-of-life preferences and there were no adverse events. Nevertheless, a referral to the site chaplain or ethicist or mental health specialist will occur to provide support and to continue to process feelings identified during the course of the intervention, if conflicts in treatment preferences for goals of care

emerge during the intervention. Processes, such as labeling feelings and concerns, as well as finding solutions to the identified problem, will be facilitated. The RAs focus on what the family members have in common, which usually is what is in the child's best interest.

If there is conflict between the wishes of the health care team for palliative care and the wishes of the legal guardian(s) that cannot be resolved during the course of the intervention, the Co-Is will consult with their site ethicist. Families may also be referred to their site ethics board. If there is an *ethical,* spiritual or religious struggle, and families expressing a desire for spiritual counseling will be referred to an appropriate spiritual counselor at the site. The PI will also consult with Kathleen Ennis-Durstine, MDiv, Senior Chaplain and Manager of Spiritual and Pastoral Care and member of the Children's National ethics board, as needed. See **Letters of Support**.

2. Adequacy of Protection Against Risks

a. Informed Consent and Assent

The proposed research has been approved by the Children's National's IRB. As this is a multi-site protocol, the Research Nurse Coordinator at Children's National will ensure the template consent form is used by each site. The Research Nurse Coordinator will ensure that annual review and re-approval of active projects has been accomplished in a timely manner and complies with regulations from the Department of Health and Human Services, Good Clinical Practice (GCP) and HIPAA guidelines.

Consent and Enrollment: Family caregivers will undergo written informed consent using *IRB-approved* documents prior to participation in any study procedures or data collection. We requested a waiver of assent for the children, as one eligibility criterion is "unable to participate in health care decision making." Children's National will maintain documentation of families' consent and waiver of assent according to institutional guidelines. Consenting participants will complete the baseline assessment followed by randomization to CSNAT (Session 1 & 2) plus Respecting Choices (Session 3) or Treatment as Usual. Follow-up sessions are at 3 months post-intervention.

Participants will be recruited by the investigators and other study personnel at Children's National Health System, following study procedures described above. If interested, in participating, informed consent will be processed. Families may take the consent form home for review. Families will be read the consent documents by study staff or if the family requests, allowed to read over the informed consent documents, and then any questions they have concerning the clinical trial will be addressed by study staff. Because one of the eligibility criteria for child participation in the study is that the child is unable to participate in decision making, we received approval from the Children's National IRB for a waiver of assent. Each family caregiver will receive a copy of his/her signed informed consent, and an additional copy will be filed in his/her child's medical records, if consistent with study site procedures.

Secondary screening by the trained RA-Assessor will be conducted following signed, written consent or at a later time, depending on the preference/convenience of the family.

b. Protection Against Risks

Dr. Lyon will be primarily responsible for protection against risks. However, protection against risks is the responsibility of all members of our research team.

Our participant sample is treatment and disease experienced. Many have participated in research studies throughout their child's life. They are quick to know if they want to do a study or not. Families

of children with severe rare diseases which have no cure and are often accompanied by co-morbidities may be at greater risk of emotional distress. In conferring with our Co-I, **Dr. Hinds**, who has conducted many studies with dying children, we will implement the following as overall guidelines:

1. "Commitment to no surprises"
    a. Hinds' research shows there is decreased likelihood of a feared distress reaction if families know exactly what is going to be done during the study. So prior to each intervention session, the family will be shown the CSNAT questions, Respecting Choices Interview, advance care planning document, and then asked if it is okay to continue;
    b. Next we will show the questionnaires etc. to family(s) if he/she would like to continue; and
    c. The RA will state, "You could be bothered by some of these questions. You have a right to say pass. You are in complete control and you can stop anytime you want."

2. If something did upset a participant, after supporting the family, the RA will ask if there is a staff person they feel comfortable with that they would like to meet with and we will contact that staff person to support the participant.

Families of children who are in the Intensive Care Unit (ICU) are very ill and will not be "bothered" by activities unrelated to their crisis. Therefore, families of children who are in the ICU will not be approached for enrollment. If a child later is discharged from the ICU, the family can be enrolled. If at some point during the study a family who has started the intervention has a child who becomes admitted to the ICU and this ICU admission occurs during a planned study visit, research staff will ask the treating physician if they feel it is appropriate to approach the parents/legal guardians about completing the study visit or reschedule based upon the severity of the admission. The treating physician, health care provider and parents/legal guardians' wishes will be respected. Each study site has a system in place to notify research staff of the death of a patient within 24 hours. This will prevent the risk that a family will be contacted about a study visit by the RA who does not know that the patient died.

<u>Adverse Events (AE):</u> We have operationalized the definition of a Serious Adverse Event (SAE) and Adverse Event using the PI developed Satisfaction Questionnaire, which we used in previous research of advance care planning with adolescents with HIV and cancer. To date our research has demonstrated no serious adverse event or adverse event, even though the process is emotionally intense.[55] These definitions were approved by our *IRB* and our Safety Monitoring Committee (SMC) for our previous studies, as the IRB thought we had too low a bar for an adverse event.

Monitoring will occur on a daily basis to review any SAs or SAEs. RAs have the PIs cell phone number and are encouraged to call directly with any concerns. Dr. Hinds is on call for Dr. Lyon whenever Dr. Lyon might not be reachable by cell. The REDCap data base has an alert built into the program if responses to the Satisfaction Questionnaire meet the criteria for an adverse event. These items were derived from community based participatory research. Participants sometimes report FACE pACP is hurtful and worthwhile, for example.[55]

Operationally Defined Adverse Event:

Careful Ongoing Monitoring for Adverse Events

Form	Name	Item	Question	Answer
16	Satisfaction Questionnaire	5	It was too much to handle	Agree/Strongly Agree
16	Satisfaction Questionnaire	7	It was harmful	Agree/Strongly Agree

Form	Name	Item	Question	Answer
16	Satisfaction Questionnaire	1	It was useful	Disagree/Strongly Disagree
16	Satisfaction Questionnaire	2	It was helpful	Disagree/Strongly Disagree
16	Satisfaction Questionnaire	6	I felt satisfied	Disagree/Strongly Disagree
16	Satisfaction Questionnaire	11	I felt courageous	Disagree/Strongly Disagree
16	Satisfaction Questionnaire	13	It was worthwhile	Disagree/Strongly Disagree

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For the purposes of this study an adverse event is when ONE of the following statements are endorsed on the . **Agree or strongly agree:**

- "It was too much to handle." OR
- "It was harmful."

AND

In addition to one of the above statements being endorsed, ALL of the following must be endorsed for an adverse event to occur**. Disagree or Strongly Disagree**

- "It was useful."
- "It was helpful."
- "I felt satisfied."
- "I felt courageous
- "It was worthwhile."

Definition of Serious Adverse Events (SAEs)

For the purposes of this study a serious adverse event will be defined as an emotional breakdown requiring hospitalization or inpatient behavioral health services for emotional distress very likely/certainly related to the study intervention.

Any serious adverse event occurring during the protocol conduct will be reported and reviewed by the PI, Dr. Lyon. Any serious adverse event will be monitored to ensure the event was actually caused by the intervention, and not some coincidental issue. These events will be collected and reported in compliance with the local IRB guidelines. The PI and *IRB* must be notified within 24 hours of the reported serious adverse event. We will discontinue the study until a corrective action plan is in place.

The PI and *IRB* must be notified not more than 5 days after becoming aware of an adverse event. Training will continue throughout the course of the study to minimize the likelihood of such an SAE.

<u>Emergency Intervention, non-protocol related:</u> Children's National is equipped with its own protocol for emergency interventions (i.e., to address signs of acute mental illness, sexual abuse, physical abuse, or neglect) that will be implemented in such circumstances. In cases of child abuse or neglect, a report will be made to Child Protective Services or the appropriate agency at each site. In every case, the legal guardian/family caregiver will keep a copy of the consent and waiver of assent forms,

which contains emergency contact information for Dr. Lyon, and other members of the multidisciplinary team. Another copy will be stored in research office that is triple-locked.

Emergency Intervention, protocol related: We are fortunate that in our setting from which participants will be recruited nurses, psychiatrists, psychologists, social workers and case managers are part of the health care team and therefore available to our research participants. There is an on-call mental health specialist or psychiatrist available 24 hours a day. Study personnel will have clinical experience and will be trained in active listening and in issues related to death and dying. Thus, the study staff and the hospital-based setting are well equipped to address participants' emotional distress. In addition to the specific study procedures to be described below, appropriate referrals will be made to participants for additional help, such as counseling, assistance with insurance coverage, housing, palliative care services and substance abuse treatment.

Families in pain or fatigued: We will stress the absolute voluntary nature of the study and offer to do the intervention or assessment on the "installment plan" breaking up the assessments to 15 minute increments if need be and/or the intervention. Families will be offered the option of discontinuing and resuming at a later time within the "protocol window" for the study visit. This leaves the option to the family to decide, respecting their choice. RAs are trained to be sensitive to the needs of patients and their families and will discontinue the study visit at a participant's request.

Families in emotional distress: There are four study phases where emotional risks will be assessed or directly observed: 1) screening for eligibility; 2) during the CSNAT interviews (Session 1 & 2); 3) during the Respecting Choices Intervention (Session 3); and 4) during the 3-month post-intervention assessments.

1. *Screening*. Following the consent/assent process, guardians/family caregivers will complete a brief screener. Participants will be informed that should the screening reveal any evidence of a significant mental health issue, they will be referred to a mental health professional at the clinic/hospital or in the community for further assessment.

Immediately following completion of all screening questionnaires, the RA-Assessor will review the potential participant's responses to identify active psychosis or homicidality or suicidality (assessed by interview using structured questions. Family caregiver endorsement of current suicidality, homicidality, or active psychosis will activate the following procedures:

- The research assistant (RA) will contact the PI to help determine if there is a clear or immediate danger. The PI is experienced in these kinds of assessments for dangerousness, or;
- If the RA cannot reach the PI, the RA will contact/page the psychiatrist/social worker on call, who will either come to the research office to assess whether or not there is a clear and immediate danger to self or others or conduct the assessment at the emergency department;
- If the on call psychiatrist cannot be reached, the RA will escort the participant to the emergency department;
- In each instance, the RA will remain with the participant until the appropriate health care provider takes responsibility for the assessment and care of the participant.

2. CSNAT. If a family member is overwhelmed by strong feelings during the CSNAT interview, we will follow the procedures below in #3.

3. Intervention. Although we had no adverse events during our FACE trial, we appreciate that despite the structure of the pACP intervention, which was designed to contain strong emotions in a

supportive, caring and respectful way, some participants may become aware of painful feelings of guilt, anger or sadness. If a family member is overwhelmed by strong feelings, the RA, who is clinically experienced and trained in active listening and affect regulation, will provide support. After support is provided the RA will ask if the family would like to continue, take a break, or reschedule for another day. We will not remind the family at this time that they can discontinue the study, as they may experience this as abandonment or punishment for expressing strong feelings. However, participants will have been told during enrollment that they may withdraw from the study at any time and will be reminded of this when confirming the next scheduled appointment.

If the family member continues to be distressed, the RA will ask if there is a staff person they feel really good about that they would like to meet with and we will contact that staff person to support the participant. If yes, the RA will stay with the family until the staff person arrives or accompany the family to the staff person's office and wait with the participant until the participant is seen.

If the family member expresses suicidal, homicidal or psychotic thoughts during the course of the intervention the procedures for managing this event will be followed as described in "1. *Screening*" from list above.

4. Assessment at 3 months post-intervention. The same procedures will be followed as described during the screening process.

To further protect against risks, we will continue with the following protections, which we put in place for our previous pediatric advance care planning studies:

1) We will hire staff with experience, maturity, good basic communication skills and good interpersonal skills;
2) RAs hired to be Interventionists who do not meet certification criteria for the RC Interview will not be allowed to interact with participants;
3) We will provide ongoing intensive and comprehensive training. For example, in addition to what was described earlier, Respecting Choices Facilitators participate in two days of multiple role plays of possible adverse events that could occur during the Respecting Choices Interview. Scenarios will be given which were known to have ever come to the attention of the ethics board at Children's National, so that we will be as prepared as possible for any eventuality;
4) The PI will meet weekly with Children's National researchers to provide support to the research team and to address any emotional reactions or concerns they (RAs) have about a new family under consideration for recruitment and enrollment or issues that arose in the course of an intervention session;
5) We have a chaplain and an ethicist available for referral to discuss spiritual struggles or to help process conflicts about treatment preferences;
6) Procedures are clearly delineated about what the RAs should do if a participant should become suicidal or homicidal or psychotic during the intervention sessions or during any of the assessments; and
7) The PI's available by cell phone. All research participants have a copy of the assent/consent form, which will contain appropriate Investigator phone numbers.

In addition to the procedures already in place, if they should prove to be insufficient, we also have an additional Co-I at Children's National, Dr. Hinds, who is an expert in safety issues in conducting research with dying children. Dr. Hinds and Dr. Lyon share an office suite at Children's National and have easy access to one another for consultations. Dr. Lyon, Co-Is and the Safety Monitoring Committee, as well as the study staff, will be responsible for ensuring that these procedures are followed and documented in the process notes and that the safety of participants is protected.

Although this study will be examining spirituality/religious experiences and beliefs, the FACE-Rare study is not a religious or spiritual intervention. We are including everyone regardless of religious affiliation. Instructions for responding to assessment measures include a statement that "Not all of these questions may apply to you. Please answer as best you can." Data on religious affiliation or no religious affiliation will be collected. If a participant gives no response, because it does not apply to him/her, the data will be coded as missing data.

Respondent Burden, defined as the subjective phenomenon that describes the perception by the subject of the psychological, physical, and/or economic hardships associated with participation in this research study,[122] has been reduced 1) by minimizing the number of questionnaires; 2) by treating informed consent as moment-to-moment for all of the participants involved in the study; 3) by ensuring that participants will feel free to decline research participation; and 4) by offering to conduct all study visits by traveling to the participant's home, by telephone or by using Telemedicine services available. In our previous studies participants felt cared about and satisfied with the benefits of participation.[5-9] During beta-testing it was not uncommon for an alarm to go off indicating the child was in need, which required the immediate attention of the family. Staff will be trained to be sensitive to these interruptions and to the goal of supporting the family.

We recognize having a treatment as usual control is a relative weakness in the design, but the burden to conducting an active comparator for control families, which will have no potential benefit, outweighed this limitation. Using a treatment as usual control is also within the norms of rigorously designed RCTs.

Informed Consent and Waiver of Assent of Family Caregivers/Legal Guardians and Patients

Only study team members trained to secure assent/consent will approach participants about the study. Written consent forms will be completed and all consent procedures will be documented according to the standard hospital procedures. All data will be kept confidential and stored in a locked file inside a locked office. Refusals will be documented in the research records and examined for any possible patterns. All participants who meet eligibility criteria regardless of gender or minority status are fully eligible to participate in this study. If they choose to enroll, the guardian(s)'s written consent will be obtained by study staff at screening for their own participation, as well as consent to have their child participate. We will request a waiver of assent for children unable to participate in health care decision making. Legal guardian(s)/family caregiver(s) may decline or withdraw from the study without penalty at any time.

All participants will receive a secondary screening. We will ask for a waiver of consent for those who decline to participate so we can gather demographic data on decliners. This will enable us to determine if there is a significant difference between acceptors and decliners. These sheets will be assigned a unique identifier number. Consent at this time will be for data collection for the child from the EHR through medical chart abstraction and from study questionnaires from the legal guardian/family caregiver at baseline assessment and 3-month post-intervention.

Consent will also include a release to give the child's primary HCP a copy of the advance care plan. A copy of the advance care plan and a summary statement of the respecting choices conversations about goals of care in a HIPPA compliant email will be given to the primary health care providers for their records. No other data will be shared with the HCP.

Assent will be waived for all child participants, as an entry criterion is being unable to participate in decision making. Legal guardian/family caregiver consent to participate (for both their child and themselves). Participants will be assessed to determine readiness to participate, to identify obstacles

to participation, and to enhance motivation. They will be given ample time to answer questions. This process is expected to take 20-30 minutes.

The consent and assent waiver forms describe the nature of the screening phase, right to refuse to answer any questions and to withdraw from the screening process at any time without penalty, methods in place to protect confidentiality, and limits of confidentiality (e.g., suicidal/homicidal intent). The consent form describes the nature of participation, rights of refusal to answer any question and to withdraw at any time without penalty, methods in place to protect confidentiality, and limits of confidentiality (e.g., child abuse/neglect, suicidal/homicidal intent).

Eligible families will then be scheduled to complete the baseline data collection session. At the completion of the baseline assessment the family/child dyad will be randomized. Dyads randomized to the intervention will then be scheduled for the CSNAT (Sessions 1 & 2) or Respecting Choices Interview (Session 3). The RA-Assessor will not be informed of randomization, to maintain blindness. The Respecting Choices Facilitator will then contact the family to confirm the Respecting Choices sessions, to explain the program in more detail and to answer any questions. The Respecting Choices Facilitator will also contact control families to let them know they were randomized to controls and that if the intervention is successful, we will offer the intervention to them at the end of the study as a clinical service. The RA-Assessor will administer all follow-up assessments at 3 months post-intervention.

Randomization will be triggered by computer following completion of the baseline assessment in the REDCap database. Employing an intent-to-treat paradigm, dyads will be randomly assigned to FACE Rare vs. TAU control, blocked by study site to control for site specific differences.

Participant Reimbursement

There will be no reimbursement for enrollment (consent), screening for eligibility or completion of the Demographic Data Sheet.

After a review of the literature,[159-165] participants will be reimbursed for their participation. To ensure that the payment does not constitute an undue inducement, particularly for our more vulnerable participants, the reimbursement is within the norm for our studies. We will reimburse at a rate of $25 per dyad per session (5 study sessions) to cover the costs associated with participation, such as parking, child care, and to minimally compensate participants for their time and the inconvenience associated with participation in research. We will provide monetary compensation using a credit card, “Clincard”, per our institutional requirements at Children’s National. Unless other arrangements have been made, reimbursement will be immediate upon completion of each assessment session. In our judgment and that of medical ethicists, monetary reimbursement for time and inconvenience is a respectful way to treat our research participants.

We recognize having a treatment as usual control is a relative weakness in the design, but the burden to conducting an active comparator for control families, which will have no potential benefit, outweighed this limitation. Using a treatment as usual control is also within the norms of rigorously designed RCTs.

The Role of the Physician or Healthcare Team Member/Follow-up Interview Activities

Physicians are not conducting the FACE-Rare Intervention. If legal guardians have unanswered questions regarding their child’s medical condition, potential complications, and benefits/burdens of life-sustaining treatment choices, they will be referred back to their physician or advance care provider to seek clarification. A postcard is given to the participant(s) with their questions on it, as a

cue to remind them to ask these questions during their next medical visit. In our previous research, participants found this empowering. Participants will be assisted in developing specific questions they have for their physician and be encouraged to discuss treatment decisions with other professionals, such as a religious advisor. Any treatment decisions made by the legal guardian will be documented in the medical record as evidence of their goals of care and treatment preferences for their child in accordance with the standard practice at each site for documenting advance care plans. No data from the primary health care provider will be collected during this study.

Protection Against Breaches of Confidentiality

Participants' data will be kept confidential. Participants will be told that they may choose not to answer any given question. No confidential information concerning patients' charts will be released to us, until patients/clients provide explicit permission by completing a signed release. At the time of consent, participants will sign a release of information to share a copy of their advance care planning document with their primary HCP. Participants will understand that this study has clinical medical purposes, as well as research purposes. They will also be informed that the completed advance care planning document from Session 3 is both a research document and a broad advance directive document and will be placed in their child's medical chart. With the exception of the primary HCP having a copy of the advance care planning document, only site research staff will have access to the participant's identity. The source documents will contain a copy of the advance care planning document. The original signed document will be placed in the child's EHR. A copy of this source document with no patient ID will be saved in a secured locked area, separate from research data. A copy will also be sent via HIPPA secured email to the child's treating/referral physician.

Consent forms will describe the nature of participation, rights of refusal to answer a question and withdrawal at any time without penalty, methods in place to protect confidentiality, and limits of confidentiality (e.g., child abuse/neglect, clear and immediate danger to self or others). Embedded in the consent documents is permission to audio or video tape, if a participant agrees.

A unique identifier number will be used on all paper surveys and for coding data on the computer. Data will be collected by the research staff and stored and locked in file cabinets in a locked office in a locked suite. The unique identifier and patient identity list will be stored in a different location from the data by the Principal Investigator, Dr. Lyon. Original audiotapes and copies will be destroyed upon completion of the study by removing them from the Children's National site encrypted SHARE File.

The study database will provide a highly structured repository to store and protect the integrity and confidentiality of study data. In addition to the study data itself, the database will house information about each protocol, including information describing each item of data collected. The stored information about each protocol will include the targeted enrollment quotas, eligibility criteria, as well as a detailed schedule of visits with information to be collected at each visit. This will enable the system to help with study management and to help improve study quality.

Finally, the database is directly accessible to standard statistical packages such as SAS, SPSS, and STATA so that interim and final analyses can be conducted without the need to transport data. This system is accessible via the internet network to investigators and their staff. Security is provided via a password-based authentication system that governs access, including a data view that will be dictated by study role. Patient confidentiality is protected by utilizing a randomly assigned ID number. Additionally, access to data that links the patient ID number to identifying is restricted. The ID number

will never be directly linked to the identifying data. See **Facilities and Resources** for details on Data Management and REDCap.

c. Vulnerable Subjects

We will be including children ages ≥1 year and <18 years, meeting the NIH classification as children (NIH Guide: NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects). This is a vulnerable and underserved group of children living with rare diseases who have been understudied and underrepresented in research.

This is a minimal risk study with the prospect of direct benefit to the children's caregivers and to the children.

Only Protected Health Information from the Electronic Health Record will be collected for the child. Otherwise, there are no procedures involving the child. Legal guardians will consent to their child's participation and sign a waiver of assent, as the study population is children unable to participate in health care decision making. The results of this study, if successful, will lead to generalizable knowledge that will improve the quality of life of family caregivers of children with rare diseases and the children themselves by providing medical care consistent with their families' treatment preferences.

3. Potential Benefits of the Proposed Research to Human Participants and Others

Potential benefits of participating in the FACE-Rare Intervention to participants include relieving caregiver distress, psychological, social and spiritual suffering, as well as maximizing quality of life. Psychological benefits include "breaking the ice" for ongoing conversations about treatment preferences as the rare disease progresses or as decisions need to be made in the face of uncertainty, given the lack of knowledge about the rare disease. Families can then be assured that they had made decisions in the best interest of their child and feel supported. Although not the primary purpose of our study, our pilot data suggests that the experience of mastery and control in the context of family support in a caring, respectful way, supporting family decision-making concerning palliative end-of-life care, strengthens families. Families will have the opportunity to enhance their social support networks through involvement with the research staff, which may diminish feelings of isolation. Child participants may also improve their linkage to care, simply through participation in the study, including enhanced connectedness with their respective clinics, benefiting from any primary or adjunct services offered by the clinics (e.g. mental health, case management).

Our previous studies indicate that the emotional intensity of these conversations for study participants, i.e. conversations involving advance care planning for their child if there were to be a bad outcome, was outweighed by the anticipated benefits to research participants and their children.

The proposed study has the potential to build an evidence base for structured pACP as one dimension of palliative care, thereby benefiting all children living with a rare condition and their family caregivers. If this R21 demonstrates initial efficacy, we plan to submit a future R01 to conduct a fully powered international trial with children with rare diseases. Furthermore, these results may provide an empirical foundation and method (FACE-Rare protocol) for relieving suffering and maximizing quality of life for all children living with a life-limiting condition who can participate in end-of-life decision making (e.g. cystic fibrosis, muscular dystrophy).

4. Importance of the Knowledge to be Gained

The major benefit of this proposed project will be to fill the gap in our knowledge about what family caregivers of medically fragile children with rare diseases want with respect to palliative care. These children may have multiple-morbidities and are unable to participate in health care decision making. Studying this heterogeneous and neglected group is consistent with the recommendations of the NIH

State of the Science Conference Statement on Improving End-of-Life Care[166] to increase the study of minorities and children who are underrepresented in end-of-life research. This study will also inform the current clinical, ethical and policy discussions as well as the legal issues in a variety of areas, such as the debate surrounding advocacy, particularly for those children with impairments in physical functioning. Careful research in this psychologically sensitive area of palliative care is also consistent with Institute of Medicine recommendations[15,167] and the NIH Roadmap intention to discourage "risk adverse" research and to encourage innovation.[168]

Our hope is that this study will provide a structured model for facilitating family decisions about end-of-life care, for those families who do not have the good fortune to have children who have the capacity to share in decision-making. The structure of the FACE-Rare model may help to contain the anxiety, sadness and anger that talking about death can provoke, meeting the goals of the NINR's campaign *Conversations Matter*.™,[103] Facilitating these discussions in a sensitive way in a clinical setting, as part of routine care, may improve quality of life and patient and family-centered outcomes by increasing the likelihood that the family's goals of care are honored in the last weeks of life for their dying child. This intervention may empower families to make their own choices regarding palliative care and to communicate these choices to their primary health care provider, thereby increasing their control in a low control situation. It will also provide us with knowledge of the impact of religion on treatment choices and quality of life for families.

As with our previous studies, we will send study results for primary outcomes to study participants in the form of a newsletter. For those patients who may die while on study, the newsletter will be accompanied by a personal letter expressing sorrow for the loss of their child and appreciation for their participation and contribution to the science of pACP. This letter will be personalized and signed by the research staff known to the patient and family.

The risks of participation in this minimal risk study are reasonable in relation to the importance of the knowledge that may result from the study.

Study participants who were randomized to the control condition will be offered the intervention while the study is in the dissemination stage, if study aims are realized. The Co-Is at Children's National are committed to this, as a study service.

Safety Monitoring Committee (SMC)

This study will be conducted in accordance with appropriate sections of the International Conference on Harmonization's Guidelines for Good Clinical Practice (GCP). The principal investigator, Dr. Lyon, will be responsible for monitoring and the process by which adverse events and unanticipated problems will be reported to all relevant regulatory bodies. See **Data Safety and Monitoring Plan** for more details.

Dr. Lyon will compile a Safety Monitoring Committee (SMC), following the guidelines provided by NINR/NIH. Dr Lyon will invite an expert in the full range of issues associated with children with serious illnesses and their families, with additional expertise in evidence-based assessment and intervention, specific to the goals of this Program Announcement to identify and meet the palliative care needs of persons with rare diseases and their families. Three additional members will be invited who are experts on quality of life measurement, data safety, and the science and ethics of research on palliative care for children.

The SMC will meet a minimum of once a year. The SMC will decide what data summaries it wants to see in order to adequately monitor the data and the safety of the patients and families in the study.

The SMC will review all adverse events, for immediate assessment of any safety concerns in the study. All serious adverse events will be reported to the PI, SMC and the IRB within 24 hours of event knowledge. Dr. Lyon will then notify the Research Nurse Coordinator, Mrs. Thompkins, who will coordinate notifications.

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