Overview of the study. We will determine the effects of HAI on reducing anxiety, depression, worry, and pain and enhancing QoL in children (n=30) (ages 8-17 years) with a LTC and their parent caregivers (n = 30-60). Human-animal interactions will involve visits from a registered canine team for 10-15 minutes during each child's potentially anxiety-producing appointments at the clinic or hospital. These appointments occur approximately once/week: Children and parent dyads will receive HAI intervention and complete measures of anxiety, depression, worry, pain and QoL at baseline, 4 weeks and at the end of the study (8 weeks).

Eligibility Criteria and Recruitment. Our sample target is 30 children diagnosed with advanced cancer and their parents/guardians. We will oversample to conservatively accommodate a drop-out of up to 35%, thus our accrual target sample is 48 children and parent/guardian pairs. Inclusion criteria for children are: 1) ages of 8-17 years, 2) diagnosed with advanced cancer as defined by any stage of relapsed, recurrent or refractory cancer as indicated by healthcare team and 3) able to understand English or Spanish to complete consents and surveys. Inclusion criteria for caregivers are: 1) parent or guardian as determined by person who brings child to >50% of their clinic visits, and 2) able to understand English or Spanish to complete consents and surveys. Inclusion criteria for animal therapy teams are: 1) registered Pet Partners or other nationally recognized agency team, 2) owner able to speak and understand English or Spanish, 3) owner who has successfully completed volunteer training at Vanderbilt University Medical Center.

Exclusion criteria for both children and caregiver include a self-reported fear of or allergies to canines or cognitive impairment as identified by healthcare team or inability to complete consenting process. Recruitment and enrollment for this study will occur over 18 months. In collaboration with each child's nurse practitioner or physician, our team will determine families eligible for the study. Final decisions regarding screening and inclusion will be determined by the PI. Approximately 200 children 8-17 years are diagnosed with cancer at MCJCHV each year and about 40 have advanced cancer. In our past study with children diagnosed with cancer, only 2 families (3.5%) of 58 families approached declined to participate with no attrition. We anticipate refusals and attrition may be higher with this population, so are very conservative in our estimates (Table 1).

Table 1. Estimates of Children Meeting Inclusion Criteria and Recruitment Rates

Children Ages 8-17 Years with Advanced Cancer at MCJCHV	Total Per Year	Total 18 Months
Number of eligible participants per year	32	48
T1: Accrual (96% in previous studies, conservative estimate for this population is 85%)	27	40
End of Study: Retention (95% in previous studies, but conservative estimate for this population is 75%)	20	30

Setting. All study activities including procedures and data collection will take place in the treatment room in the hematology/oncology clinic or a private room at MCJCHV and will occur approximately weekly. Sessions will coincide with children and families' scheduled medical appointments or inpatient hospitalizations.

Procedures. After potential participant families are identified and screened for inclusion/exclusion criteria, the PI or project coordinator will meet with the primary caregiver, introduce the study, and review the IRB-approved consent. If the parent/guardian agrees, the child will be approached for assent. Participants will then be asked to complete baseline measures. Human-Animal Interactions will occur at each clinic visit or hospitalization, as long as they are not more frequent than weekly. Data collection will occur at baseline, 4 weeks, and study end (8 weeks) with children and parents completing surveys in private sections of the room. All study data will be stored in REDCap, a secure, web-based application for building and managing databases. Tablets will be used by study participants to enter their responses to study measures into their study record in REDCap. Paper forms will be available to participants if there is a problem with network connectivity or if the participant prefers that form. Subsequently, data on paper forms will be double-entered into the participant's record in REDCap by trained study staff and verified.

Human-Animal Interactions (HAI). Every effort will be made to ensure the same dog is used consistently with each family, but a back-up team will be available in the event the HAI team is ill or unavailable. The HAI consists of the following: 1) *Social Interaction*: participants will be guided by the canine owner in interfacing with

the dog and 2) *Activities*: participant-selected activities from a core group of 22 activities such as petting the dog and talking to the dog, chosen by Pet Partners to constitute the foundation for HAI. Pet Partners is a non-profit organization that assists individuals to maintain their health or regain their full potential through HAI.[35] Activities used represent integration of interactions into a child's treatment plan. Implementation fidelity of intervention and receipt of intervention will be determined by documentation by the animal handler, a trained research assistant, and the PI after reviewing the video recordings of HAI**.**

Implementation Fidelity: As recommended by the NIH Behavior Change Consortium, we will use 5 key factors to enhance HAI fidelity: study design, provider training, HAI delivery, treatment receipt (patient understands or is able to use the new skills), and enactment (patient treatment skills in the intended situations and at the appropriate time).[36, 37] In addition to following the activity log developed by Pet Partners for the HAI, we will maximize fidelity through 1) comprehensive initial training for all canine owners, 2) reviewing videos recorded at each session, 3) monthly research team meetings to review recruitment, protocol activities, and

intervention fidelity, 4) content analyses of interviews and 5) re-training as necessary. *Safety*: Any evidence of aggressive behavior by the dogs will be carefully monitored and the interaction will end immediately with the removal of the dog from the premises. At the end of a family's 2-month participation in the study, we will ask children and parents separately: "Please describe what it was like to participate in this project." Results will provide a positive transition at study end and offer feedback and potential revisions to be used in the next study. Children will received a stuffed dog at the conclusion of the study to provide continued support when they transition away from HAI.

Measures. Measures are described here and in Table 2 according to specific aims.

Aim 1: Examine feasibility of HAI sessions for children with a LTC and a primary caregiver, specifically to: a) identify and document necessary modifications for a safe and feasible intervention, b) obtain recruitment estimates and determine potential recruitment barriers, c) evaluate elements of implementation fidelity (design, training, delivery/receipt of treatment, enactment), and d) verify safety.

Safe and feasible intervention: Safety verification will be determined by documentation of any evidence of potential risk for injuries encountered during the sessions. Handler and Site Coordinator Self-Report Measure/Animal-Assisted Therapy (AAT) Activity Log is a checklist for recording people present and activities conducted during session to be completed after each session**.** *Recruitment estimates and potential barriers to recruitment*: Screening Checklist includes numbers of children meeting inclusion criteria, number recruited, and barriers.

Aim 2: Determine the preliminary efficacy of HAI sessions for 1) children with a LTC for the outcomes of QoL, anxiety, depression, worry, and pain, 2) caregivers of children with a LTC for the outcomes of stress and anxiety.

The Family Demographic Form has 14 items including questions about age, race, gender, diagnosis, family members and pet ownership. Similar to other studies and as used in our previous studies, anxiety will be measured using the 20-item STAI for Children. This questionnaire has been used extensively in school-aged children (Cronbach's alpha=.82-.87).[36] Health-related Quality of Life will be measured by the PedsQL Generic (Cronbach's alpha = .88) and Cancer (.72) report forms. The PedsQL is a 23-item (general) or 27 item (cancer) health-related quality of life questionnaire for child self-report. [38, 39] This study will use the Child Self Report and Parent Proxy versions for ages 8-12 and 13-17. The multidimensional scales include physical (5 items), emotional (4 items), social (3 items), and school functioning (3 items) dimensions with scores of 0-4 for each item for the general Peds QoL, and 8 dimensions (pain-2 items, nausea-5 items, procedural anxiety-3 items, treatment anxiety-3 items, worry-3 items, cognitive-3 items, perceived physical appearance-3 items, and communication-3 items for the cancer Peds QoL. *Caregiver:* The Pediatric Quality of Life (PedsQL) Generic Parent (Cronbach's α=.93) and Cancer (.87) inventories have parent report forms that range from 21-27 items.[38] The State-Trait Anxiety Inventory (STAI) Adult Form assesses primary caregivers' anxiety, has a reported Cronbach's alpha ranging from.78-.82 and includes 20 items in Likert format to assess trait characteristics and 20 items for state anxiety.[40] A brief new measure of depression from the Patient Reported Outcomes Measurement Informastion System (PROMIS) with strong psychometrics has been added for child self-report and parent-proxy (Cronbach's α=.80).

Exploratory Aim: To explore mechanisms (reduced salivary cortisol and urinary norepinephrine levels) associated with 8 weeks of HAI.

Mechanisms and biomarkers: As part of our exploratory aim we will measure salivary cortisol and 24 hour urinary norepinephrine (NE) levels. Studies have shown that increase in salivary cortisol and urinary NE correlate to increased levels of acute stress.[41, 42] Similar to the methods of Corbett et al.[43] salivary swabs will be obtained at baseline at 10:00 am and 2:00 pm before HAI and 30 minutes after HAI on week 4 and week 8 of the study. Attempts will be made to schedule appointments between 10:00 am and 2:00 pm to control for circadian variations. Saliva will be obtained and stored ((-80°C) until time of analysis in the Vanderbilt Hormone Analytical Services Core. Urinary NE will be measured from 24-hour urine collections obtained at baseline, midway, and toward the end of the study. Twenty-four hour (NE_{24}) levels will be used as an indirect measure of stress and adrenergic activation. Urinary creatinine levels will confirm compliance with 24-hour collections, and variations in volume. NE values will be compared to normative ranges for sex, ethnicity, and BMI. NE will be measured by high performance liquid chromatography (Quest diagnostics). Although not primary outcomes, we will measure heart rate/blood pressure, using a calibrated Dynamap monitoring device. Evidence from our work with newly diagnosed cancer patients indicates anxiety and worry may begin to

increase at the time families realize the HAI sessions are ending. Therefore as noted above, we will obtain these measures at baseline, mid-way at 4 weeks, and at the end of the 8 week study. Part of Aim 1 is to determine the feasibility of the HAI intervention, especially the most reliable time to obtain these measures.

Table 2. Measures and Schedule

Variable	Measure	# items/Scoring Range Clinical Significance	Time to Complete	Schedule
AIM 1			Minutes	
Safety/Feasibility	AAT Activity Log	22 items	5	After each HAI
Feasibility	Recruitment Rate, Attrition			Consent/assent. After final HAI
Intervention	Videotaping of All Sessions		15	During each HAI
AIM 2	**Children**			
Anxiety –Trait	State-Trait Anxiety Inventory for Children (STAIC) Trait Form	20 items/20-80; Clinical significance 39-40	5	Baseline
Anxiety – State	STAIC State Form	20 items/20-80; Clinical significance 39-40	5	Baseline, 4 & 8 wks
QoL	PedsQL-General	23 items/range 0-92	15	Baseline, 4 & 8 wks
	Peds QL-Cancer	27 items/range 0-108		Baseline, 4 & 8 wks
HR and B/P	Heart Rate and B/P Log		2	Baseline, 4 & 8 wks
Depression	PROMIS Depressive Symptoms	8 items	2	Baseline, 4 & 8 wks
Acute Stress	Salivary Cortisol		3	Baseline, 4 & 8 wks
	Urinary NE, creatinine		20	Baseline 4 & 8 wks
HAI Perceptions	Open-Ended Interview	Semi-Structured	15	End of Study
	Parent			
Child QoL	Family Demographic Form	14 items	10	Baseline
	PedsQL General and Cancer-Parent Proxy	26 items	5	Baseline, 4 & 8 wks
Anxiety – Trait	STAI – Trait Form (Adult)	20 items/20-80; Clinical significance 39-40	5	Baseline
Anxiety – State	STAI –State Form (Adult)	20 items/20-80; Clinical significance 39-40	5	Baseline, 4 & 8 wks
Depression	PROMIS Depressive Symptoms Parent Proxy	6 items	2	Baseline, 4 & 8 wks
HAI Perceptions	Open Ended Interview		15	End of Study

Data Management. Dr. Dietrich (Co-I, VUSN biostatistician) will provide support for: (a) the development of REDCap database for study measures and materials, (b) data management, and (c) statistical analyses.
Participation status will be tracked for all enrolled child/parent participants, and monthly 'Expectation Reports' indicating outstanding assessments will minimize loss of data. Information (e.g., age, reason for non- participation) from eligible participant who do not consent will only be used in summary form to describe the recruitment process. Team training will include all investigators and staff at the initial team meeting and booster sessions as needed to ensure data collection consistency, quality assurance, and intervention fidelity. The PI will provide study manuals, including scripts with instructions, and lead bi-weekly team meetings to maximize recruitment, fidelity, and safety. Questionnaires will be

electronically administered in a standard order with written instructions. Study coordinator or research assistant help will be available in-person to clarify instructions to participants and answer any questions about items. Dr. Dietrich will develop scoring programs and score all measures. Item ranges, and missing and unusual values, will be double-checked.

Statistical Analysis. Analysis of the feasibility and preliminary effects of human-animal interactions (HAI) on child and parent stress, depression, anxiety, and quality of life will be conducted using SPSS and STATA statistical software. Descriptive statistical and graphical methods will be used to summarize and visualize patterns in the study outcome data distributions at each time of assessment. Simple group comparisons of participation and retention (e.g., differences in demographic, clinical characteristics) will be conducted using Chi-Square tests of independence and Mann-Whitney tests. Reliable change indices (RCI)[44-46] will provide the critical foundation for summarizing and analyzing overall efficacy, as well as characteristics of the participants most likely to benefit from HAI in future work. While effect sizes will be more important than statistical significance in this feasibility study, all tests of statistical significance will maintain a maximum $p < .05$.

Table 3. Study Timeline

Study Timeline	Year 1				Year 2			
Activity/Quarter	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Hiring/training personnel, IRB approvals, database								
Enrolling participants								
Data collection								
Data analysis								
Knowledge dissemination and future grant development								

Summary, Limitations, and Future Directions: This pilot/exploratory study will evaluate feasibility, safety, and preliminary efficacy using HAI with children diagnosed with a LTC, but is not generalizable beyond children with advanced cancer. Clear strengths of this proposal include 1) inclusion of children, parents, and canines; 2) qualitative (video recordings, interviews) and quantitative (surveys, physiologic measures) data; 3) use of both established and innovative measures with this population, and 5) expertise of investigators. Collection of physiologic, survey, and observational data will provide a rich view of the experiences of HAI from viewpoints of children with cancer, parents, and animal handlers. This novel design with multiple methods will begin to fill a gap in the literature related to HAI with children with advanced cancer and will lead to future larger studies with other LTC. Infrastructure, institutional support, physical resources and a collaborative research team with established funding history ensure successful completion.

The proposed sample size in this study reflects the number of participants that can reasonably be recruited and followed in this very vulnerable population. The focus will be on generating reliable estimates of characteristics of children and parents who benefit most from this intervention. The subsequent grant will involve multiple sites with English and Spanish-speaking populations and preliminary conversations with several large children's hospitals are ongoing and yielding positive responses.

Dissemination: Results will be disseminated through at least 3 presentations at professional conferences, such as the American Academy of Hospice and Palliative Medicine and Hospice Palliative Nurses Association Annual Assembly, International Congress on Palliative Care, Society of Pediatric Psychology, National State of the Science Congress on Nursing

Research, and Oncology Nursing Society National Conference on Cancer Nursing Research. Our main form of dissemination will be through several peer-reviewed publications in multidisciplinary journals and will include manuscripts related to: (1) outcomes of childhood anxiety, depression, worry, pain, and QoL (2) parent outcomes of anxiety, stress, and quality of life, and (3) participants' qualitative reports on their experiences with HAI.

Data Safety and Monitoring Plan:

A. Monitoring Entity or Who Will Monitor the Study: The data and safety monitoring plan will follow NIH policy guidance. Based on this study being minimal risk and conducted at a single site, a Safety Monitoring Committee (SMC) consisting of at least two (2) experts who are not co-investigators or consultants on this study will be established at Vanderbilt University at the beginning of this research. SMC membership will follow NIH policy. The SMC will serve as an independent advisory board to both the PI and to the NICHD Director. The SMC will oversee the activities related to implementing the study to ensure patient safety, conformance to the study protocol, overall performance of study components, and integrity of the data being collected. SMC members will not have close current or recent affiliations with the study, will not have been directly involved in protocol development, nor supervise persons who are so involved. We will make every effort to include an independent investigator and biostatistician. As soon as possible after each SMC meeting, but within 20 days following each SMC meeting, the SMC will provide the PI with a copy to provide to the NICHD Director or designee, a written recommendation along with justification related to continuing, changing, or terminating the study. The PI will be responsible for submitting any necessary reports to the NICHD.

B. Procedures for:

B1 a) Monitoring study safety to include monitoring schedule: The SMC will meet a minimum of once a year to review study progress through informal evaluation of existing data. For each SMC meeting, reports will be prepared and provided to SMC members by the PI. Data will be provided in a manner to protect the confidentiality of subjects. The SMC will prepare an annual safety report, summarizing the efforts and findings of the Committee.

B1 b) Auditing selected cases for compliance with IRB requirements: The SMC will annually audit selected cases for IRB compliance with study procedures.

B1 c) Conformance with informed consent requirements: The SMC will annually audit consent and assent documents and study conformance with related requirements.

B1 d) Verification of source documents: The SMC will verify that study record-keeping includes documenting the existence of the subject to substantiate data collection integrity.

B1 e) Investigator compliance: The SMC will annually review all study investigators' compliance with human safety training.

B2) Minimizing research-associated risk: The SMC will monitor study data for effectiveness and safety to protect participants from exposure to unreasonable or unnecessary research risks. SMC members will review interim data in the context of the most recent scientific literature, and ensure that the study does not continue beyond the point when the study objectives have been met and a clinically meaningful answer of importance to the scientific community and the public has been obtained.

B3) Protecting the confidentiality of participant data: The SMC will review study plans for and establish specific guidelines for data and safety monitoring, including confidentiality of participant data (e.g., location of data storage.)

C. Procedures for Identifying, Reviewing, and Reporting Adverse Events and Unanticipated Problems to the IRB and NINR. Any adverse events occurring during the course of this study will be collected, documented and reported by the PI (Dr. Gilmer) to the SMC, along with reporting to the NICHD and institutional review boards as required. As soon as possible after each SMC meeting but within 20 business days following each SMC meeting, the SMC will provide the PI and the NICHD with a statement, where appropriate, concerning the impact of the study of individually observed or cumulative adverse events. Although not anticipated, if any 1 event is identified that may have caused any type of harm to a participant, study accrual will be immediately halted until the study team and SMC can review the event and determine if any study procedures need to be revised. Study accrual will only resume after review of study protocol has been completed and any recommended revisions made as suggested by the SMC.

D. For Multi-Site Studies, Procedures to Ensure Compliance with Monitoring Plan and Reporting Requirements across Study Sites. N/A - as this is a single site study.

E. An Assessment of External Factors or Relevant Information (i.e., Developments in Literature, Results of Related Studies) that May jave Impact of Participant Safety or on Ethics for Research Study. The SMC will review published reports of related studies submitted by the study investigators or SMC members to determine any external factors which may impact participant safety or ethics for our study. The SMC will determine whether the monitored study needs to be changed or terminated.

F. The Advanced Plans for Interim and/or Futility Analysis: Given the low risk of any negative impact of the intervention, as well as the considerable variability commonly seen in study outcomes, we will not reduce study statistical power by including an interim or futility analysis. Subsequent research will be greatly benefited by the proposed analysis that will make use of the full sample recruited in this study.