Canines and Childhood Cancer

Pilot Study Report

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American Humane Association and Zoetis wish to dedicate this report to the memory of Dr. John C. New, Jr. of the College of Veterinary Medicine at the University of Tennessee in Knoxville. Dr. New was instrumental in helping us implement the CCC Study, and was a constant source of knowledge, collaboration, kindness, and inspiration. He will be dearly missed.

Background and Rationale

Since December 2010, the Pfizer Foundation and Zoetis have sponsored American Humane Association (AHA) in developing and executing an innovative research study – the *Canines and Childhood Cancer (CCC) Study* – to investigate the impact of animal-assisted therapy (AAT) on pediatric oncology patients, their families, and the therapy dogs who visit them. The goals of this collaboration are to promote innovation, evidence-based research, practice improvements and knowledge advancement to further the field of research on human-animal interactions and the treatment of cancer in children. Ultimately, a better understanding of the effects of AAT on pediatric oncology patients will enhance treatment for children with cancer and their families.

In collaboration with both children's hospitals and universities across the country, AHA and Zoetis have completed a comprehensive needs assessment and have piloted a research study to inform the design and implementation of a full clinical trial scheduled to begin in late 2013. This report outlines the findings and lessons learned from the pilot study that concluded in June 2013.

Before beginning the pilot study, a comprehensive literature review was conducted (www.caninesandchildhoodcancer.org), as well as focus groups and interviews with pediatric oncology patients, parents of children with cancer, hospital staff, and animal-handlers who visit with their therapy dogs in pediatric healthcare settings. A summary of literature review, focus group, and interview findings is presented here to provide the background and rationale for the study.

At any given time in the United States, more than 40,000 children are undergoing cancer treatment, with nearly 13,500 new diagnoses made each year (Children's Oncology Group, 2013). According to the National Cancer Institute (NCI) at the National Institutes of Health (2013), cancer is the leading cause of death by disease among children aged 1 to 14 years. Encouragingly, while the incidence of childhood cancer has increased slightly over the past 20 years, mortality rates have drastically decreased with 5-year survival rates currently near 83 percent – a 25 percent jump since 1975 (NCI, 2013).

Still, quality of life for childhood cancer patients, survivors, and their families remains a concern. As childhood cancer is a "family disease," it often affects patients, parents/guardians, siblings, and extended relatives in profound ways. Findings from the *CCC Study's* literature review, as well as focus groups and interviews with hospitals, show that children with cancer and their families not only cope with physical concerns, but are also prone to psychosocial and behavioral issues including stress and anxiety, trauma, depression, loneliness, and strain in their significant relationships (Fotiadou, Barlow, Powell, & Langton, 2008; Norberg & Boman, 2008).

While the physical effects associated with the disease and its treatment may greatly improve for these children with time, psychosocial effects often linger and negatively impact cancer survivors and their families for the long-term (Michel, Rebholz, von der Weid,

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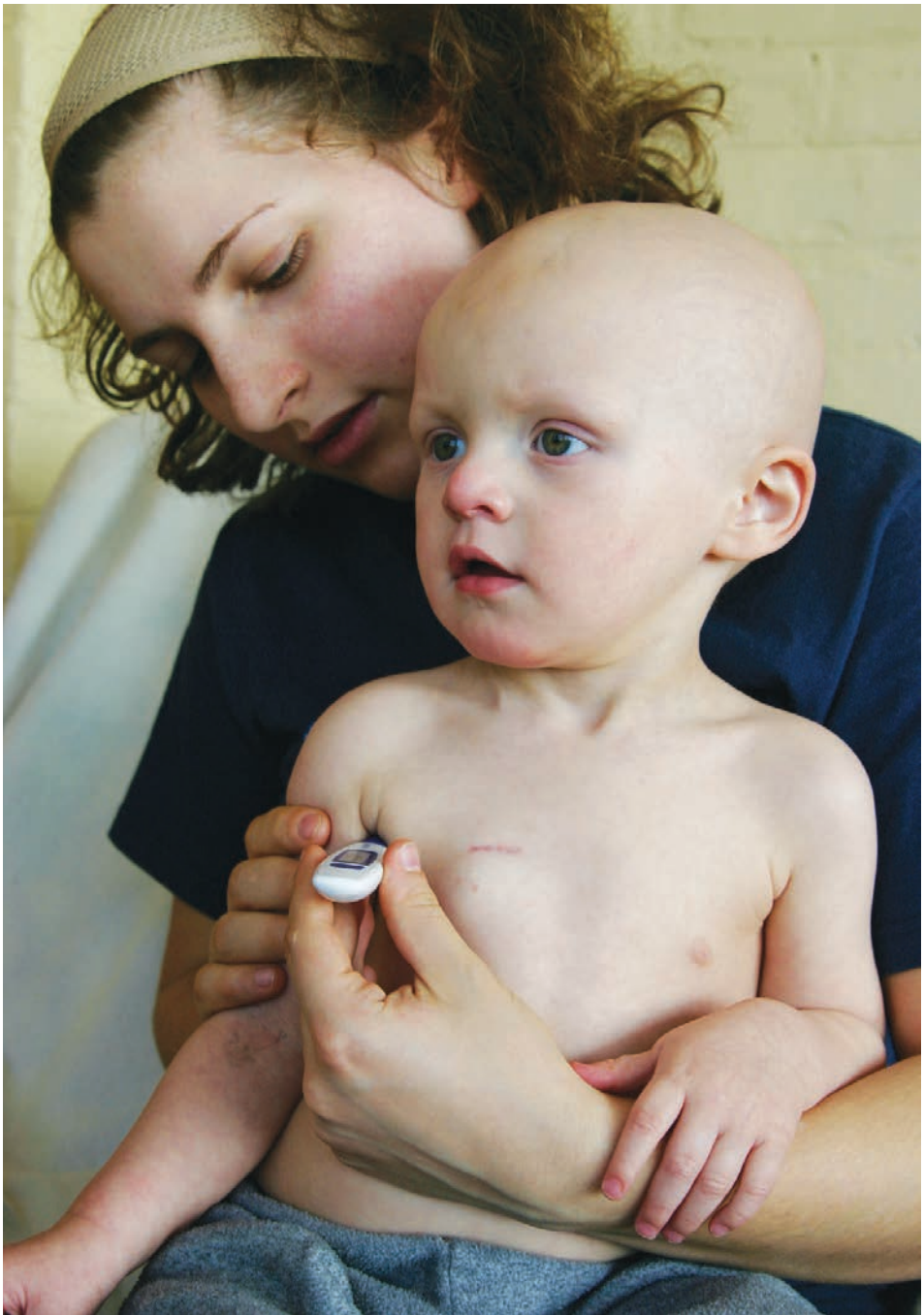
Bergstraesser, & Kuehni, 2010). Yet few evidence-based studies have either critically examined or recommended adjunctive interventions to help the entire family cope with these issues during the childhood cancer experience.

AAT, defined as a goal-directed intervention that involves a trained animal to aid in a person's healing process, is an adjunctive intervention that has promise for children with cancer and their families. Not only is AAT accessible and affordable, but research also suggests that animals can provide numerous benefits for people from all ages and walks of life (Endenburg & van Lith, 2011; Nimer & Lundahl, 2007). Reported benefits of AAT include reduced stress and anxiety; decreased blood pressure and heart rate; distraction from worry or pain; unconditional support and acceptance; increased opportunities for physical touch; improved social skills that lead to healthy relationships; enhanced self-esteem; and increased motivation to actively participate in treatment (Fine, 2010; Friedmann, Son, & Tsai, 2010; McCardle, McCune, Griffin, Esposito & Freund, 2011).



While many studies have documented the benefits of AAT, the majority of these findings have largely been anecdotal and the field has consistently struggled with developing and conducting rigorous research (Johnson, Odendaal & Meadows, 2002; Kazdin, 2010). Many argue that this lack of evidence-based research has hindered the ability of AAT to be recognized as a viable treatment option for people in need, particularly by those in the research, funding, and healthcare fields (Palley, O'Rourke, & Niemi, 2010). Although therapy dog programs are common in children's hospitals throughout the United States, existing evidence concerning the effectiveness of AAT in pediatric oncology settings is very limited. In addition, there is a general lack of scientific research on how AAT may impact the therapy animals.

Overall, there are crucial gaps that must be filled if animal-assisted interactions are to be considered effective, safe and ethical modes of adjunctive treatment. Thus, the *CCC Study* has the potential of not only advancing knowledge in both the pediatric oncology and AAT fields through rigorous and groundbreaking research, but more importantly, may greatly improve childhood cancer treatment by lending credibility to an adjunctive treatment modality aimed at providing the comfort of a therapy dog to children and families who need it now.

Pilot Aims

Due to the complicated and exceptional nature of conducting rigorous AAT research across multiple pediatric healthcare settings, it was necessary to first pilot the study in order to fully prepare for a clinical trial.

The goals of the pilot study were to:

- Address the feasibility of conducting a randomized control trial utilizing AAT within multiple pediatric healthcare settings
- Determine how to address issues of scientific integrity and protocol fidelity
- Determine the appropriateness and feasibility of the instruments chosen to measure distress across the three populations (patients, parents/guardians, and therapy dogs)
- Develop recommendations for optimization of the protocol leading up to a final research protocol for a full clinical trial

The hypotheses that were developed based on the findings of the comprehensive needs assessment are as follows:

- H_1: Pediatric cancer patients with Acute Lymphoblastic Leukemia (ALL) who receive AAT will experience less distress throughout the course of their treatment sessions than patients who do not receive AAT.
- H_2: Parent(s)/guardians of pediatric cancer patients with ALL who receive AAT will experience less distress throughout the course of their child's treatment sessions than parent(s)/guardians of patients who do not receive AAT.
- H_3: Participating therapy dogs will exhibit minimal distress over the course of the *CCC Study*.

Methods

The pilot study was conducted for six months – between January and June of 2013, with data collection lasting between three and four months, depending upon the hospital site. It was designed and implemented as a multi-site, randomized controlled study with the control cohort receiving the standard-of-care for ALL and the study cohort receiving standard-of-care plus AAT visits.

Prior to the study implementation at each site, the study design and protocol underwent Institutional Review Board (IRB) and Institutional Animal Care and Use Committee (IACUC) review at American Humane Association and each site, as appropriate. Once approval was obtained from each site, the study coordinators began their recruitment efforts. Once a child and family were determined to be eligible for the study, the coordinator approached them with the appropriate consent/assent forms to determine their interest in the study.

Sites

Two sites participated in the pilot study: East Tennessee Children's Hospital, in conjunction with the University of Tennessee's College of Veterinary Medicine, in Knoxville, TN and St. Joseph's Children's Hospital in Tampa, FL.

Population

The patient population for the pilot was defined as children ages 3 through 11 years who were newly diagnosed with ALL or who had been in treatment for ALL for no longer than 12 months and whose parent/guardian gave their consent to participate in the study and, if appropriate depending upon age, gave their assent to participate in the study. Based on admissions data from each of the two pilot sites, the research team anticipated that up to six patients (or three patients per site) would participate in the six month pilot trial.

The patient population was selected for the following reasons:

- ALL is the most common form of childhood cancer
- ALL patients typically experience a common treatment protocol under the Children's Oncology Group (COG) that is consistently used at both sites enrolled in the pilot study
- Aside from consistently utilized medication, ALL treatment does not involve procedures that may directly impact neural function or development
- Age 3 is within the peak age range for diagnosis of ALL

Common activities during AAT sessions are petting, giving the dog a treat and asking the dog to do his/her obedience cues such as 'sit' or 'down.'

The parent/guardian population for this study consisted of parents/guardians of eligible child patients, as determined by the above criteria and who consented to participate.

The therapy dog population for this study consisted of registered therapy dogs of animal-handlers who regularly visited one of the pilot sites, attended a training regarding the pilot study protocol, and consented to participate.

Randomization

Consent and assent forms completed by families agreeing to participate in the study were uploaded to AHA's secure File Transfer Protocol (FTP) site. Once the AHA research team received the form, the child and family were randomized into either the control group (standard-of-care for ALL) or the treatment group (standard-of-care plus AAT).

Study Protocol

A variety of physiological and psychological measures were used to compare the levels of distress experienced by the patients and their parents/guardians in the control and study cohorts. Those children and parents/guardians assigned to the control cohort completed measures and/or were videotaped at designated time points, described later in this document, during their regularly scheduled treatment sessions at the hospital. The children and parents/guardians in the study cohort completed the same measures as those in the control cohort and/or were videotaped at designated time points during their regularly scheduled treatment sessions at the hospital.

Animal-handlers were asked to collect their dog's saliva at five different points in time at the beginning of the study to establish a baseline measurement, and then again after each 20 minute session with the child and family. Saliva was collected to measure cortisol, a biomarker for stress in dogs. Likewise, handlers completed a self-report form on their dog's behavior and activities that occurred during the session after each visit with the child and family. Finally, the dog's behavior during the session was videotaped at designated time points throughout the pilot study for comparison with their salivary cortisol levels and handler-documented behavior.

Intervention

Those children and parents/guardians assigned to the study cohort were paired with one animal-handler team and received AAT visits approximately once a week over the course of the pilot study. A back-up handler was assigned to fill in if the primary handler was not available. Visits with the therapy dog and handler lasted approximately 20 minutes and the handler was trained to end the session earlier if they felt their dog was becoming stressed. In order to achieve the goal of measuring AAT as it is implemented every day in children's hospitals across the country, the activities performed during the intervention were chosen at the discretion of the handler, based on the dog's abilities and interests. Common activities during AAT sessions are petting, giving the dog a treat and asking the dog to do his/her obedience cues such as 'sit' or 'down.' Handlers were asked to log the activities that were conducted during the study session. All of the AAT visits and data collection throughout the pilot study occurred in the outpatient or infusion clinic settings.

Measures and Instrumentation

The following measures were utilized for children who participated in the pilot study:

- Observational Scale of Behavioral Distress (OSBD): a scale developed to measure children's responses to painful medical procedures. Video cameras were used to record sessions so that the AHA research team could document the child's behavior utilizing the OSBD.
- Polar RS800CX training watch with Polar WearLink W.I.N.D. transmitter: to measure heart rate variability throughout a study session.
- Blood pressure cuff: to measure systolic and diastolic blood pressure at the beginning and end of a study session.

The following measures were utilized for parents/guardians:

- State Trait Anxiety Inventory (STAI): a questionnaire that differentiates between current state anxiety and more inherent trait or character anxiety.
- Pediatric Inventory for Parents (PIP): a questionnaire to specifically measure stress in parents/guardians who are dealing with a critically ill child, particularly a child with cancer.
- Polar RS800CX training watch with Polar WearLink W.I.N.D. transmitter: to measure heart rate variability throughout a study session.

The following measures were utilized for therapy dogs:

- Handler self-reports: regarding the dog's behavior, the dogs' and family's reaction to the session, activities that took place during the session, session participants, and other pertinent notes. Most of the questions are posed with Likert scale-type answers.
- Salivary cortisol: handlers collected their dog's saliva at five different points in time to develop a baseline measurement after they consented to participate in the study. They then collected their dog's saliva after each study session and those cortisol levels were compared to their dog's baseline measurement. Saliva was collected by having the dog chew on a six inch cotton swab for up to five minutes. The saturated swab was then stored in a vial in a designated freezer until shipped to an offsite lab for analysis.
- AAT ethogram: video cameras were used to record sessions so that the AHA research team could document the dog's behavioral cues utilizing the AAT ethogram.

Results

Demographics

Patients: a total of six children were enrolled in the pilot study, which was consistent with the predicted number based on admission rate. Three children were enrolled at each site. At St. Joseph's Children's Hospital, two were enrolled in the treatment group and one in the control group. At East Tennessee Children's Hospital, two were enrolled in the control group and one in the treatment group.

Parent(s)/Guardian(s): a total of six parents were enrolled in the study, one per child who participated.

Animal-Handler Teams: a total of nine animal-handlers consented to participate in the study and collected their dog's saliva for the baseline measurement. Based on the number of eligible children, four animal-handlers and their therapy dogs participated in the study sessions.

Findings

Children

Heart rate variability was collected from children once every two months; once at their first study session and then again two months later for a total of two collections. Throughout the course of the pilot, this equipment was viewed as intrusive for patients and onsite study coordinators had difficulty obtaining the data due to a variety of factors, including the chest straps being too large for many of the children.

Blood pressure was collected from children at the beginning and end of the study session, once every two months. Like the heart rate variability, it was collected at their first study session and then again two months later. Some children did refuse to have their blood pressure measured at times; however, this procedure is common for the children and study coordinators and was not seen to be as intrusive as the heart rate variability.

The Observational Scale of Behavioral Distress (OSBD) was utilized once every two months via video recordings of the study sessions; once at their first study session and then again two months later. This scale is intended for use during stressful medical treatment procedures. After going through IRB reviews at the pilot sites, hospital sites determined that the therapy dogs would not be allowed to visit during these types of procedures due to sterility concerns. However, it was still necessary to pilot this instrument to determine if it could be used to detect any potentially distressful child behaviors during times when the dogs were allowed to visit. After viewing the videos while utilizing the OSBD, the research team determined that the scale was not useful for the study given that each child did not display any of the distressful behaviors included in the OSBD in any of the videos, regardless of their cohort (treatment or control).

Parents/Guardians

The State Trait Anxiety Inventory (STAI) was collected from the parents/guardians once every two months; once at their first study session and then again two months later. A total of five out of the six parents/guardians completed the STAI at the first session and two parents/guardians completed the STAI two months later.

It was found that the state anxiety scores for the treatment group were slightly higher at time 1 than they were for the control group. Also, there was a very small drop in the scores for the two parents in the treatment group at time 2 compared to time 1. However, given the small sample size and lack of time 2 measurements for parents in the control group, no definitive conclusions can be drawn at this point.

Average Tx Group Time 1	36
Average Tx Group Time 2	35.5
Average Ctrl Group Time 1	30.5

The Pediatric Inventory for Parents (PIP) was collected from the parents/guardians once every two months; once at their first study session and then again two months later. Like the STAI, a total of five out of the six parents/guardians completed the PIP at the first session and two parents/guardians completed the PIP two months later.

There are a total of 10 scales on the PIP, including Communication, Medical Care, Emotional Distress, Role Function, and overall Frequency and Difficulty. Each of these PIP scales has two components: 1) the frequency in which a difficult event occurred and 2) the level of difficulty that event presented. For the purposes of addressing the hypothesis regarding parents/guardians, the research team was most interested in the Emotional Distress scale. Two sample questions/events from the Emotional Distress scale are as follows: "Seeing my child sad or scared" and "Thinking about my child being isolated from others." Parents were asked to circle first how frequently the event had occurred for them in the past seven days (How Often: 1=Never, 2=Rarely, 3=Sometimes, 4=Often, 5=Very often) and then were asked to circle how difficult that event was for them (1=Not at all, 2=A little, 3=Somewhat, 4=Very much, 5=Extremely).

	Emotional Distress Frequency	Emotional Distress Difficulty
Average Tx Group Time 1	53.7	52.7
Average Tx Group Time 2	59.5	55
Average Ctrl Group Time 1	42.5	43.5

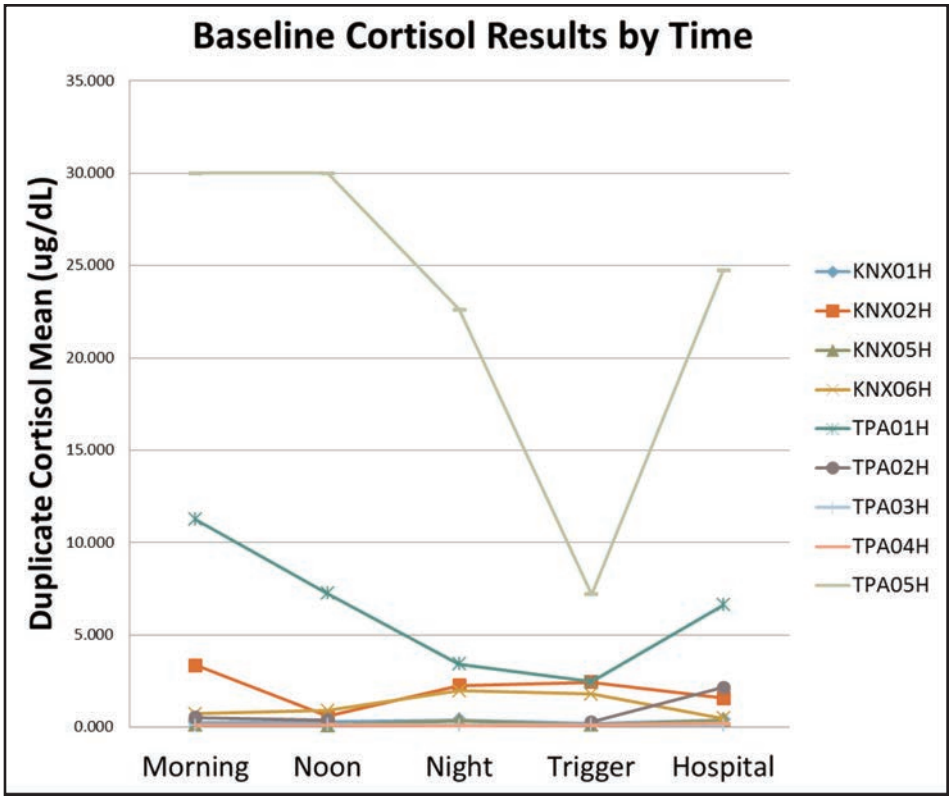
It was found that the scores for the treatment group were slightly higher at time 1 than they were for the control group. Also, there was a very small increase in the scores for the two parents in the treatment group at time 2 compared to time 1. However, given the small sample size and lack of time 2 measurements for parents in the control group, no definitive conclusions can be drawn at this point.

Heart rate variability was collected from the parents/guardians once every two months; once at their first study session and then again two months later. Throughout the course of the pilot, this equipment was viewed as intrusive for parents (i.e., they had to tell the onsite coordinator their height/weight/age and affix the strap around their chest) and onsite coordinators had difficulty obtaining the data due to a variety of factors. Like with the patient population, this instrument was not found to be feasible over the course of the pilot study.

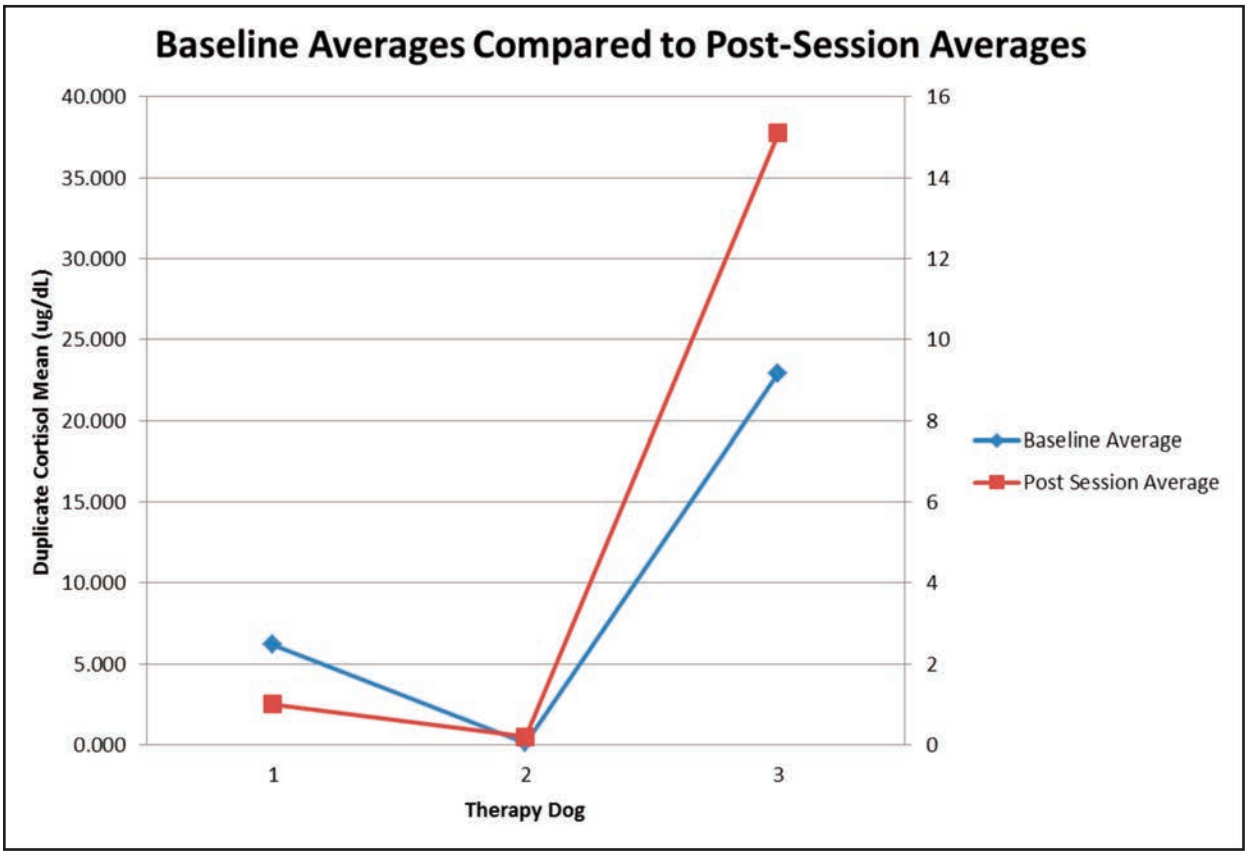
Animal-Handler Teams

To obtain a canine's baseline salivary cortisol measurement for comparison to post-session cortisol levels, handlers collected their canine's saliva on a non-working day at the following time points:

i. Upon waking ("morning")
ii. Mid-Day ("noon")
iii. Evening, prior to typical bedtime ("night")
iv. Approximately 20 minutes after the introduction of a known "trigger," such as the canine seeing his/her therapy vest/bandanna or visit bag ("trigger")
v. Approximately 20 minutes after arriving at the hospital around the time of day that they would typically visit ("hospital")



Preliminary data from nine canines shows that there is a considerable amount of variation at the five time points. The average "morning" cortisol level tended to be the highest, with the "hospital" samples eliciting the second highest levels and the "trigger" time-point producing the lowest levels.



Data from three canines showed that there is also a considerable amount of variation between dogs in their post-session cortisol levels. For example, it was found that two of the three canines had lower levels of post-session cortisol, on average, than their baseline averages. Conversely, one canine had a slightly higher post-session average (0.21 µg/dL) than their baseline average (0.12 µg/dL). In general, most post-session levels tended to fall within the range of the baseline samples.

A total of 14 handler-self reports were completed after study sessions. An additional nine sessions were scheduled across patients, however, due to child illnesses, refusals to visit/interact, absences and/or scheduling difficulties for the patient or handler, these visits did not take place. There was very good compliance by the handlers in completing the self-report measure after each study session. The average session duration was exactly 20 minutes. Some sessions were slightly shorter with a minimum of 11 minutes, while some sessions were slightly longer with a maximum of 24 minutes.

In answering the Likert scale-type questions in the post-session surveys, handlers indicated that their dogs were very eager to interact with the patient during the therapy sessions, with an average rating of 4.29 out of 5. However, the handlers indicated that the parents (3.54) and children (3.07) were not as eager to interact with the dog throughout the entirety of the session.

When handlers were asked to assess how distressed the children and parents were when they arrived to the treatment session, as well as after the interaction with the dog, the handlers indicated that there was very minimal distress from all participants (1.60 for children at arrival and 1.60 for children after interaction out of a possible 5; 1.70 for parents at arrival and 1.80 for parents after interaction out of a possible 5).

Most handlers indicated that their dog was not tired after the study session, with an average rating of 2.2 out of 5. Handlers indicated that the sessions were slightly more beneficial for the children than for the parents, with average ratings of 3.8 (for children) and 3.43 (for parents) out of 5. The following table shows the items, rating scales and the average ratings of each item discussed above.

Question	Scale Ratings (1-5)	Average Handler Rating
How eagerly did your dog want to interact with the patient during this therapy session?	1=clearly did not want to interact; 5=extremely eager to interact	4.3
How much did the patient interact with your dog during this therapy session?	1=did not interact at all; 5=did not stop interacting	3.5
How much did the parent/caregiver interact with your dog during this therapy session?	1=did not interact at all; 5=did not stop interacting	3.1
How distressed did the child seem upon your arrival with your therapy dog?	1=not distressed at all; 5=extremely distressed	1.6
How distressed did the parent/caregiver seem upon your arrival with your therapy dog?	1=not distressed at all; 5=extremely distressed	1.7
How distressed did the child seem AFTER interacting with your therapy dog?	1=not distressed at all; 5=extremely distressed	1.6
How distressed did the parent/caregiver seem AFTER interacting with your therapy dog?	1=not distressed at all; 5=extremely distressed	1.8
How tired do you think your therapy dog was immediately following this visitation session?	1=not tired at all; 5=extremely tired	2.2
Overall, how beneficial do you feel your dog's visit was for the child today?	1=not beneficial at all; 5=extremely beneficial	3.8
Overall, how beneficial do you feel your dog's visit was for the parent/caregiver today?	1=not beneficial at all; 5=extremely beneficial	3.4

In just more than half of the sessions (8), handlers indicated that they noticed signs of stress in their dogs at some point during the session. Most often, a lack of the study participants interacting with the therapy dog was noted as being a stressful event for their dog.

The most frequently noted participants in the therapy session included the child and the parent/guardian. Often, the child life specialist or a nurse would be present but did not necessarily "participate" in the session every time.

Talking to the dog and petting the dog were the most common activities cataloged by the handlers. Playing with one of the dog's toys, taking photos of the dog, and getting stickers of the dog were the other most frequently cataloged activities that took place during the study sessions.

A total of four study sessions with two children (time 1: first study session and time 2: two months after the first study session) were recorded for purposes of using the AAT ethogram to examine canine behaviors. A total of three frequency scales were used in the ethogram: distance seeking behaviors, contact seeking behaviors, and aggression. There are also four duration scales used: active, sitting, laying and passive.

There were some observed behaviors in the videos that were indicative of canine stress, such as panting, restlessness, lip licking, and looking to the handler for guidance or direction. Encouragingly, the handler self-reports from those sessions indicated that the handlers were also aware of these types of behaviors and their probable connection to stress in their dogs. It became apparent throughout the video coding process that 20 minutes may be too long for the AAT sessions, as the number, nature and frequency of distance seeking behaviors among dogs tended to intensify with session length (i.e., in sessions lasting longer than ~15 minutes).

Twenty minutes also seemed particularly long for younger children; this may be due to their limited attention spans and/or their stages of development. Across all videos, there were no aggressive behaviors (e.g., growling) observed. There were a number of positive, affiliative behaviors (e.g., tail wagging) that were observed which were not on the existing AAT ethogram that the researchers felt were important to capture going forward. Therefore, an updated AAT ethogram was developed for the full trial based upon the observations and findings from the pilot.

Discussion

By examining the progress made and lessons learned in the *CCC* pilot study, it is clear that each of the goals of the pilot (outlined on page 5 of this document) were met. There are several important findings related to each pilot goal that will inform the optimization of the full trial study design, as well as ensure that the full trial is implemented in a successful and rigorous manner.

Goal 1: Address the feasibility of conducting a randomized control trial utilizing AAT within multiple pediatric healthcare settings

The research team found that it was feasible to conduct a randomized control trial utilizing AAT at both of the pilot sites. Integral to the implementation and feasibility of the pilot study were:

- Support of the study's goals from the hospital and pediatric oncology department;
- An established AAT visitation program with committed animal-handler teams;
- A dedicated staff member who was able to coordinate schedules, as well as collect, upload, store and ship the data/specimens on a regular basis;
- Back-up handlers and staff members who were willing to fill in when necessary;
- Protocol-specific training of staff and handlers prior to the start of the pilot;
- Regular communication on study progress between the site participants and AHA research team;
- Consultation from sites, Zoetis, and other partners on addressing any challenges that arose.

Goal 2: Determine how to address issues of scientific integrity and protocol fidelity

Scientific integrity was ensured throughout the course of the pilot study due to the involvement of, and approval from, four separate Institutional Review Boards (IRBs) and two separate Institutional Animal Care and Use Committees (IACUCs). These approvals and subsequent oversight ensured that both the humans and animals involved in the research study were treated humanely and ethically throughout the duration of the study. All AAT standards, as well as program and hospital requirements, were upheld by the animal-handler teams and their certifying organizations at all times. At no point were there any adverse events that required action on the part of any site for either the human or animal participants.

There were a few challenges related to protocol fidelity that were uncovered during the pilot study. These were resolved on a case-by-case basis, as appropriate, and were incorporated into protocol and training modifications for the full trial design as necessary. For example, one issue related to protocol fidelity concerned the length of AAT sessions. While handlers adhered strongly to the 20 minute suggested timeframe for their sessions, it was noted that 20 minutes was often too long for either the dog or the child participant. This is an important finding because it will be necessary to adjust the timeframe for the full trial to ensure the well-being of both the therapy animals and the human participants.

Additionally, procedures related to proper data collection methods (i.e., ensuring the completion of all forms by participants, recording all designated sessions via proper camera use, and arranging for a back-up staff member to collect data when necessary) were not always consistently followed. Therefore, modified training materials will be developed for the full trial to ensure that project staff members are fully informed and comfortable with all of the data collection procedures.

Goal 3: Determine the appropriateness and feasibility of the instrumentation chosen to measure distress across the three populations (patients, parents/guardians, and therapy dogs)

In addressing this goal, it was found that some of the selected instruments worked well, while others were not feasible or useful based upon the populations and design elements of the pilot study.

In examining the patient measures, the OSBD was not found to be a useful measure due to the timing of the AAT visits. The OSBD is intended to rate child behaviors observed during stressful and/or painful treatment procedures. However, upon implementation of the pilot study, the research team was informed that AAT visits would not be allowed to occur during stressful procedures. Similarly, the patients in the control group had their study sessions scheduled at times when they were not undergoing stressful procedures. Therefore, behaviors included on the OSBD were not exhibited by any of the participating children in the pilot study, and the instrument was not determined to be useful for examining distress in the patients participating in the *CCC Study*.

The full trial will last for approximately 12 months, with each enrolled patient and family participating in weekly sessions for four months.

The Polar RS800CX training watch and Polar WearLink W.I.N.D. transmitters for evaluating heart rate variability were found to be infeasible due to the intrusiveness of the devices, as well as the difficulties staff encountered in utilizing the devices. Conversely, blood pressure was found to be an appropriate and feasible way of measuring physiological distress in the children. Previous studies, conducted in a variety of other settings, have measured lower blood pressure in subjects when a dog is present versus without a dog (Barker & Wolen, 2008; Friedmann, 1995; Tsai, Friedmann, & Thomas, 2010).

In examining the parent/guardian instruments, the STAI and the PIP were both found to be appropriate and feasible measures for evaluating distress; compliance on both measures was quite high and no reported problems were reported. As with the patient population, the heart rate variability monitors were found to be infeasible due to their intrusive and difficult nature.

In investigating the therapy dog measures, it was found that the salivary cortisol instrumentation and processes were both appropriate and feasible in evaluating stress in the participating dogs, both in the design of the baseline collection as well as the post-session collection times. With training and practice, most handlers became accustomed and/or comfortable with collecting saliva from their dogs. In some cases, handlers thought the process was stressful for their dogs, and made adjustments to their collection routines accordingly. For example, one handler determined that the clinic room where she collected the saliva was stressful for her dog and decided to change this location to the AAT volunteer office. She found that her dog was much more calm and comfortable during the saliva collection process in the new location. Regular and open communication with handlers will be important to continue during the full clinical trial.

The animal-handler self-reports were found to be feasible, but in need of modification. Asking handlers to rate the "success" of the sessions was determined to be inappropriate since their primary focus and role is to ensure the safety and well-being of their therapy dog. For example, asking them to rate the level of distress that the human participants experienced is not appropriate since handlers are not trained human services professionals. Other sections of the handler self-report, including a listing of the participants and activities that took place during the session, were found to be both appropriate and feasible.

Finally, the AAT ethogram was found to be feasible, but in need of modification. The AHA research team was able to properly code the videos using the ethogram, however there were some positive and affiliative behaviors that were observed but were not included on the existing instrument. Additionally, depending upon the behavior, it was difficult to know how to consistently note each behavior (in terms of duration and/or frequency) and to interpret behavior scores using the pilot ethogram.

It was therefore determined that this ethogram needed to be modified for the purposes of the *CCC Study*, as it was difficult to utilize reliably and tended to primarily focus on negative or aggressive behaviors that are rarely seen from highly trained therapy dogs. An ethogram with a balanced roster of behaviors has been developed for use in the full clinical trial. As behavior ethograms specifically for therapy dogs do not currently exist, the research team collaborated with animal behavior experts on the creation of this cutting-edge research tool.

Goal 4: Develop recommendations for revisions to the protocol leading up to a final research protocol for a full clinical trial

After careful consideration of the pilot findings, the research team has developed an updated and optimized protocol for the full clinical trial to address lessons learned during the pilot study. The following modifications were incorporated into the full clinical trial design:

The patient population was updated to expand the diagnosis criteria beyond ALL. Rather than designating specific diagnoses, participants will be children with cancer who have been recently diagnosed (within the past 30 days) and are undergoing a regular schedule of outpatient chemotherapy as the primary eligibility criteria, with a slightly expanded age range of 3-12 years. The full trial will last for approximately 12 months, with each enrolled patient and family participating in weekly sessions for four months. These expanded eligibility criteria and four month data collection periods will aid the research team in reaching the enrollment target of 132 patients across all sites and in having adequate statistical power to ensure study rigor.

Due to the lack of distress indicated and exhibited by the pilot population, the hypotheses have been modified slightly to focus on stress/anxiety for patients and parents/guardians and health-related quality of life for patients. The updated hypotheses for the full clinical trial are as follows:

H_1: Pediatric cancer patients undergoing a consistent, regular chemotherapy treatment regime who receive AAT will experience less stress/anxiety and will have an improved health-related quality of life (HRQOL) throughout the course of their treatment sessions than patients who do not receive AAT.

H_2: Parents/guardians of pediatric cancer patients undergoing a consistent, regular chemotherapy treatment regime who receive AAT will experience less stress/anxiety throughout the course of their child's treatment sessions than parents/guardians of patients who do not receive AAT.

H_3: Participating therapy dogs will exhibit minimal distress over the course of the *CCC Study*.

The AAT protocol has been shortened to 15 minutes (+/-5 minutes) to address the issues related to dogs and/or the patients becoming stressed, tired or disinterested in AAT sessions lasting 20 minutes.

The most significant changes to the full trial study design concern the measures and instrumentation schedule that will be utilized. For the patients, the OSBD and the heart rate variability monitors will no longer be used. Instead, the State Trait Anxiety Inventory – Children (STAI-C), the Pediatric Quality of Life InventoryTM (PedsQL), and pulse will be added to the instrumentation. Blood pressure will continue to be measured. The frequency of the data collection will also be increased. The STAI-C, pulse and blood pressure measures will be used on a weekly basis. The

PedsQL will be used at the time of enrollment into the study and on their final session (four months after enrollment).

For the parents/guardians, the heart rate variability monitors will no longer be used, but the STAI and PIP will continue. As is the case with the patients, the frequency of the measures will be increased. The STAI will be used on a weekly basis and the PIP will be used on a monthly basis. The

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parents/guardians will also be completing a parent proxy of the STAI-C weekly, as well as a parent report form for the PedsQL at the time of enrollment and then again at their final study session (four months after enrollment).

For the animal-handlers/therapy dogs, the handler self-report, salivary cortisol and ethogram will again be utilized. While the salivary cortisol collection will remain the same as the pilot (5 baseline samples and weekly post-session samples), the handler self-report and the AAT ethogram will be modified. The handler self-report has been modified to focus on the participants (i.e., who was present) and the activities that occurred during the AAT sessions; their ratings of the amount of interest, stress and distress among human participants have been removed to help ensure that their focus is on their therapy dog and not the other session participants.

The AAT ethogram has been modified to include additional positive and affiliative behaviors. Finally, an additional instrument will be utilized for animal-handlers at the time of enrollment into the study. The Canine Behavioral Assessment and Research Questionnaire (C-BARQ) will be used to gain a better understanding of each dog's individual temperament as rated by their handler. This additional instrument will increase the understanding of the completed ethograms and salivary cortisol data as they relate to the amount of stress that a particular dog may be experiencing throughout the duration of the study.

Overall, piloting the research design was a successful venture for the *CCC Study*. Each goal established by the research team was met, and several important lessons were learned throughout the process. Further, the findings gleaned from the pilot study will inform the research team in successfully preparing and implementing a rigorous clinical trial in five pediatric healthcare settings across the U.S. – a true trailblazer in the field of AAT practice and research. The participating sites are:

- St. Joseph's Children's Hospital in Tampa, FL
- Monroe Carrell Jr. Children's Hospital at Vanderbilt in Nashville, TN
- Randall Children's Hospital at Legacy Emanuel in Portland, OR
- UC Davis Children's Hospital in Sacramento, CA
- UMass Memorial Children's Medical Center in Worcester, MA, in partnership with Cummings School of Veterinary Medicine at Tufts in North Grafton, MA

Upon the conclusion of the *CCC Study's* full trial, it is predicted that our findings will help the practice of AAT gain the respect and recognition it deserves – as a credible, viable, and effective treatment option for children with cancer and their families. Likewise, by completing the pilot study of this groundbreaking research, AHA and Zoetis are now one step closer to providing evidence on the healing power of human-animal relationships and the important role these bonds can play for children and families in need of support.

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