Helping Improve Pediatric Patient Outcomes (HIPPO)

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Protocol

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PROTOCOL TITLE:
The HIPPO Study: Helping Improve Pediatric Patient Outcomes

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1.0 Objectives

This study involves three phases.

Phase 1 is a small feasibility study with the objective to develop and optimize a method for measuring the microbial levels on children's hands that is comfortable for this study population. The optimized method will be used in Phases 2 and 3 of the study.

Phase 2 is a randomized controlled trial to assess the efficacy and safety of therapy dog visits for children with cancer. This study has the following specific objectives:

1) To assess the effect of therapy dog visits on psychosocial outcomes and satisfaction with care among pediatric oncology inpatients.
2) To determine whether therapy dog visits increase microbial levels on children's hands.

We hypothesize that therapy dog visits will reduce patient distress, lower treatmentrelated anxiety, increase happiness, and improve satisfaction with hospital care. We further hypothesize that therapy dog visits (including standard hand sanitization with alcohol-based gel) will not increase microbial levels on children's hands.

As a secondary aim, we will examine the immediate effect of therapy dog visits' on parent/guardian anxiety.

Phase 3 is an observational study to describe microbial levels before a dog visit, after a dog visit but before hand cleaning, and after hand cleaning. This phase will provide additional information for Aim 2 that cannot be obtained during Phase 2 given the nature of the Phase 2 design.

2.0 Background

Animal-assisted interventions are increasingly common but evidence about their safety and efficacy is limited. Pediatric oncology patients are an important population in which to study animal-assisted interventions. Children with cancer experience significant distress, and though they are often resilient, strategies to improve their symptoms, hospital experience, and health-related quality of life are needed.[1-9] In other (non-cancer) pediatric populations, animal-assisted activities (AAA) generally reduce pain,[10,11] provide comfort,[12-14] and have positive emotional effects.[15] A prior pilot study on AAA in pediatric oncology[16] and our own data suggest AAA benefits pediatric oncology inpatients. In preparation for the current study, we successfully completed a pilot study at Seattle Children's (R03CA169576; PI: Chubak; SCH IRB # 15702), which demonstrated the need for and feasibility of this research. We recruited 19 pediatric oncology inpatients at Seattle Children's Hospital to receive a one-time therapy dog visit. The intervention consisted of an unstructured visit (≤20 minutes) by an experienced therapy dog team

(dog + human handler). The primary outcome was changes in PedsQ™ Present Functioning Scales scores.[9] Mean age was 12.9 years (standard deviation [SD] = 3.6; range 7–18; median 12.8) and participants were split evenly by gender (10 males, 9 females). After the intervention, distress levels (total PedsQL score) were lower than before the visit.[17] We observed large and statistically significant decreases in worry and tiredness, and smaller but significant changes in fear, sadness, and pain. With a small sample and no comparison group, we could not evaluate pathogen transmission in the pilot study.

A rigorous randomized controlled trial is needed to investigate these preliminary findings. Evaluating the safety of AAA for pediatric oncology patients is also critical. Our survey found that 8 out of 19 top pediatric oncology centers do not offer AAA, mainly because of concerns about infection.[18] To our knowledge, there are no data on pathogen transmission associated with AAA visits in pediatric oncology units. Rigorous research on both the efficacy and safety of AAA is needed.

In the current study, we will test whether therapy dog visits reduce distress, lower treatment-related anxiety, increase happiness, and improve satisfaction with hospital care, and whether these visits transmit pathogens. Regardless of our findings, this study will provide hospitals and care providers with data for making evidence-based decisions about offering AAA to this population of patients. If rigorous research demonstrates AAA to be safe and effective, AAA programs could improve care experiences for pediatric oncology patients nationwide. If our results support safety concerns about therapy dog visits or indicate they may not improve psychological health, our study will stimulate further research on new strategies to increase AAA safety and efficacy for pediatric oncology inpatients.

Prior to starting the randomized controlled trial of therapy dog visits (Phase 2), we first plan to optimize our method for hand sampling (Phase 1). We will conduct a small feasibility study to ensure our hand sampling technique is comfortable and appropriate for the population we plan to enroll. The sampling method we plan to use is based on studies performed on adults so it is important to ensure it is appropriate for children and modify it if necessary. Phase 3, an observational study of patients receiving therapy dog visits, will provide additional information for Aim 2 that cannot be obtained during Phase 2.

3.0 Inclusion and Exclusion Criteria

All phases of the study will enroll patients who are admitted to the Cancer Care Unit (Forest 7 and 8) at SCH and have a diagnosis of cancer. A member of the SCH study team will review the Cancer Care Unit census to identify potential participants and medical record review will be performed to confirm eligibility. Once a potential participant is identified, the study team will contact the patient's clinical oncology team or bedside

nurse to confirm eligibility and ensure the clinical team/bedside nurse agrees it is appropriate for the patient to be invited to participate in the study.

If eligible and interested, patients may participate in multiple phases of the study.

The parent/legal guardians of participants who are enrolled in Phase 2 of the study will also be invited to participate in surveys.

Patient inclusion criteria (all phases)
This study will enroll English-speaking patients aged 5-17 years admitted to the Cancer Care Unit (Forest 7 and 8) and who are on the oncology service with a diagnosis of cancer irrespective of specific oncologic diagnosis, sex, race, and ethnicity.

Patient exclusion criteria
Patients will not be eligible to enroll if they:

- Are allergic to dogs or have a sensitivity to dogs
- Are afraid of dogs
- Are on the bone marrow transplant service
- Have isolation precautions in place per Infection Prevention policies (e.g. viral respiratory precautions, contact precautions, etc.)
- Skin on hands not intact (e.g. moderate to severe eczema involving the hands or other generalized skin breakdown)
- Have no English-speaking parent/legal guardian
- Have no parent/legal guardian able to provide written consent
- For phase 3 only, unwilling or unable to pet the dog with both hands.

Parent/legal guardian inclusion criteria
Parent/legal guardians of children enrolled in Phase 2 of this study will be invited to participate in baseline, discharge, and follow-up surveys. The child's participation is not contingent on the parent/legal guardian's participation. One English-speaking parent/legal guardian per patient will be eligible to participate as long as they are able to provide written consent and it is appropriate to include them (e.g., the parent/legal guardian is not estranged from the child, there are no social work concerns).

Special populations
All phases of this study will enroll individuals who are not yet adults (children aged 5-17 years). We will also enroll adult parent/legal guardians of children enrolled in Phase 2 of this study, and some mothers or other female legal guardians may be pregnant. Study procedures for parent/legal guardians only involve responding to surveys and will therefore not pose any risk on the pregnancy.

We will not enroll adults who are unable to provide consent, wards of the state, or prisoners.

4.0 Study-Wide Number of Subjects

N/A

5.0 Study-Wide Recruitment Methods

N/A

6.0 Multi-Site Research

N/A

7.0 Study Timelines

Phase 1:

- Duration of individual patient participation: 1 day
- Planned enrollment: 10 patients over 1 month
- Data collection completion: 1 month

Phase 2

- Duration of individual patient and parent/legal guardian participation will vary. Patient may receive study visits for up to 4 weeks after enrollment. These visits will take place during hospitalizations that occur during this period. A final follow-up survey will be collected approximately 9 weeks after discharge from the first hospitalization that occurred during the study period. The timing of this hospital discharge will vary between participants.
- Planned enrollment: Up to 50 patients over approximately 9 months. Up to 50 parents/guardians of these patients may participate over the same period.
- Data collection completion: 3 months after the end of recruitment

Phase 3:

- Duration of individual patient participation: 1 day
- Planned enrollment: Up to 20 patients over 2 months.

- Data collection completion: 2 month

Our approximate date for completion of the primary analyses is March 1st 2019.

8.0 Study Endpoints

Primary endpoint for Phase 1
- Successful optimization of a hand sampling method to be employed in Phase 2 and 3

Secondary endpoints for Phase 1
- Microbial levels before and after hand sanitizing + glove juice

Primary endpoints for Phase 2
- Aim 1: Patient distress post-visit as measure by the PedsQL Present Functioning Scales total score
- Aim 2: Microbial levels on patients' hands post-visit

Secondary endpoints for Phase 2
- Aim 1: Patient and parent/legal guardian responses to the instruments outlined in section 9 below, including individual scales and emotional distress summary scores from the PedsQL Present Functioning Scales
- Aim 1: Pre- to post-visit changes in distress measures
- Aim 2: Clinically important pathogens as outlined in section 9 below
- Aim 2: Pre- to post-visit changes in microbial levels on patients' hands

Primary endpoint for Phase 3
- Microbial levels on hands before and after a petting therapy dog

Secondary endpoints for Phase 3
- Clinically important pathogens after petting therapy dog

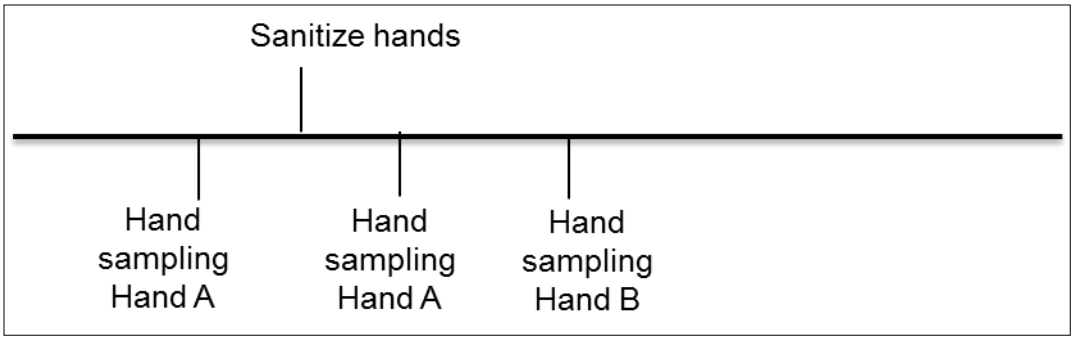
9.0 Procedures Involved

Study procedures are in addition to standard of care and no study procedures will preclude or delay standard of care.

Procedures for Phase 1
Phase 1 of the study is a small feasibility study that will involve a one-time hand sampling and survey. Specific procedures are detailed below.

After informed consent/assent has been obtained, study staff will perform a one-time hand sampling via the glove juice method of both of the patient's hands (see specific procedures described below under Phase 2): one hand will be sampled prior to hand

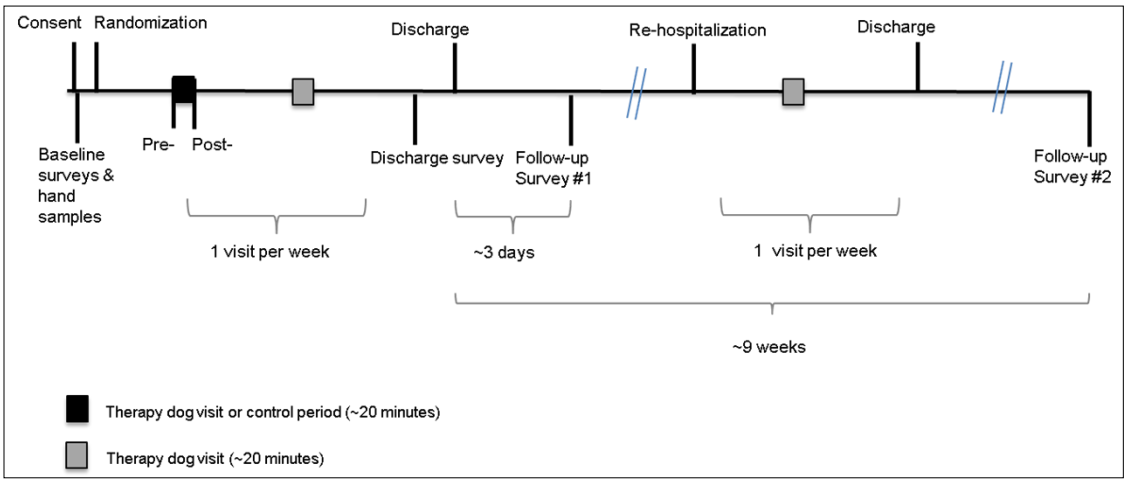
cleaning (A) and both hands will be sampled after hand cleaning (A and B). Following the hand sampling procedures, we will ask patients to provide feedback on their experience with the glove juice hand sampling. We will also ask the patient (or their parent/legal guardian) to tell us which is the child's dominant hand, when the child last bathed, and when the child last washed their hands.



Study staff will review the patient's medical record to abstract basic patient demographics, hospital admission date, cancer diagnosis, information on bathing, and receipt of any antibiotics or antifungals in the past 7 days.

Procedures for Phase 2

Phase 2 is a randomized controlled trial in which patients will be randomized to either the intervention (therapy dog visits) or control (usual care). All patients will complete a baseline survey and hand sampling and answer questions from study staff (e.g., about pets at home, which hand is dominant). Parents will also complete a baseline survey. Patients in the intervention group will receive therapy dog visits. At the first therapy dog visit after enrollment, we will collect visit-level psychosocial measures and perform hand sampling. Participating parents will also complete a survey. Similar procedures will be performed on usual care patients. Patients in the intervention group will receive subsequent dog visits ~1x/week if there is sufficient dog team capacity. At hospital discharge, ~3 days post-discharge and 9 weeks post-discharge, we will administer surveys to patients and their parents in both groups. Specific trial procedures are described in detail below in the following sections: ***randomization, intervention, control, and data collection.***



Randomization

Informed consent/assent will be performed for patients who agree to participate in the study and preliminarily meet eligibility criteria. After informed consent/assent has been obtained, baseline surveys will be administered (see Table below) and hand samples will be collected. The study staff will then assess the patient's ability to tolerate and willingness to perform future psychological assessments and hand samplings. Patients willing to proceed with the study will be randomized to either the intervention arm (visits from a therapy dog) or the control arm (no visits from a therapy dog). Participants will be randomized (1:1) to each group and stratified by age (≥13 vs <13 years). Participants will maintain their randomization assignment during any subsequent hospitalizations that occur during their participation in the study.

Intervention

Participants randomized to the intervention arm will receive a visit or visits from a therapy dog (goal: ~1x/week if dog team capacity allows) during their hospitalization and during any possible subsequent hospitalizations that occur during the study period. Study staff will review patient records to determine whether they are eligible for the intervention (e.g., not in isolation, etc.) on each day therapy dog sessions are offered. This information will be recorded.

This study will employ experienced therapy dog teams (dog and handler) who participate in the Therapy Dog Program at SCH, which already visits other clinical units at SCH. Therapy dog visits will be approximately 20 minutes in length. Activities during the visit will be at the discretion of the patient and the dog handler. Activities include petting the dog, watching the dog perform a trick, and talking with the dog handler. All activities will follow the existing regulations and procedures for therapy dogs at SCH, including instructions for proper hand hygiene. Study staff will supervise visits.

Control

Control arm patients will receive usual care. Study staff will review patient medical records before their first visit to determine if they would be eligible for an intervention visit (e.g. not in isolation) had they been randomized to the intervention group. This data is needed to assess their comparability with the intervention group.

We believe the control arm is ethically acceptable because not receiving a visit from a therapy dog is the standard of care: therapy dogs are not currently allowed on the Cancer Care Unit. Furthermore, this protocol does not expose control patients to excess risk.

Data collection

Data will be collected by direct observation, surveys, hand sampling, and medical record review.

Direct observation

During each patient's first intervention visit, the study staff will record activities that occur on a paper form, as we did in our pilot study. If the patient refuses a therapy dog session, we will record information in the same manner as for control patients.

During first visits that occur without the therapy dog (i.e., all control arm patients plus intervention arm patients who refuse a therapy dog session (or become medically ineligible for one), study staff will wait outside the room and record who enters and leaves the room (e.g., child life staff, visitors.)

Questionnaires

Patients enrolled in both the intervention and control arms will answer survey questions at various time points (Table below). Parent/legal guardians will be asked about their children's feelings and emotions. Parent/legal guardians and patients will be asked about their hospital experiences and anxiety.

The baseline surveys, pre- and post-visit surveys, and discharge surveys, will be administered by SCH staff in person. The protocol for administering the discharge and follow-up surveys is described at the end of the data collection section.

Timing of survey instruments					
Instrument	**Baseline (prerandomization)**	**1st visit Previsit**	**1st visit Postvisit**	**Discharge**	**Follow-up**
PedsQL Present Functioning Scales	C	C	C	-	-
Positive and Negative Affect Schedule	P	-	-	P	P

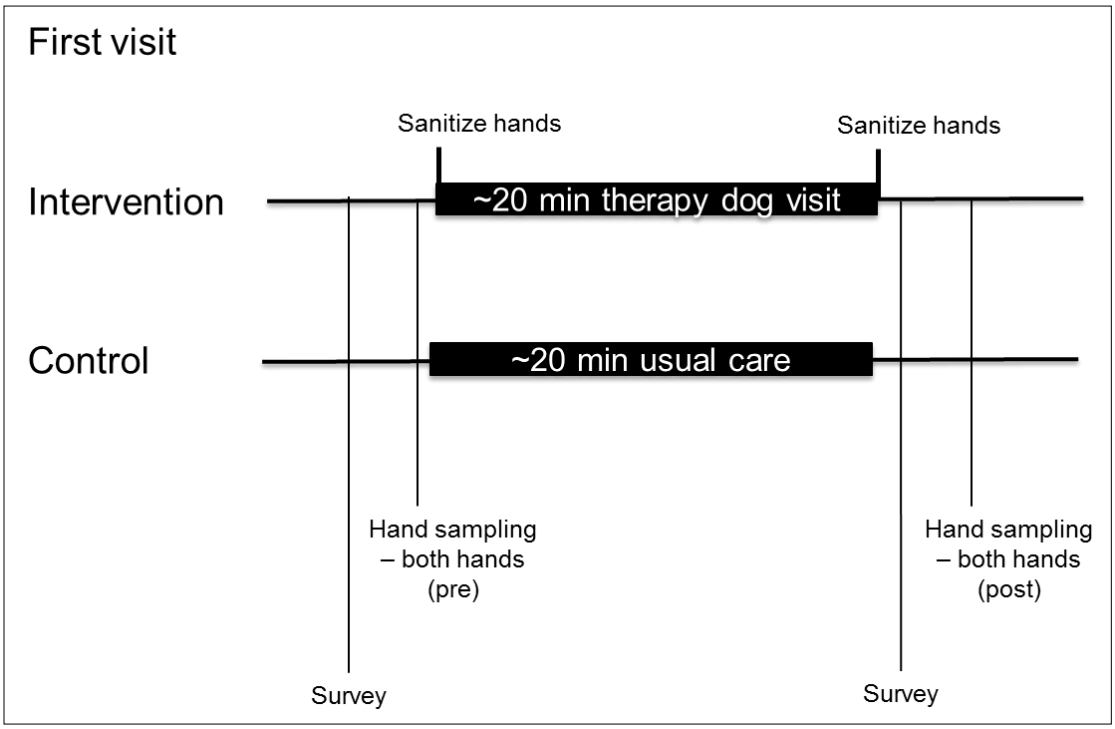
[PANAS] short versions					
Hospital rating item from the CAHPS® Child Hospital Survey	-	-	-	P	P
Questions about being in the hospital				C/P	C/P
PedsQL Cancer Module	5-7* y/o: P 8-17* y/o: C	-	-	5-7* y/o: P 8-17* y/o: C	5-7 y/o*: P 8-17 y/o*: C
Spielberger State-Trait Anxiety Inventory (6 item)	P		P		
Respondent: C = child; P=parent/legal guardian; y/o = years old; * Based on age at enrollment					

Hand sampling

All patients (those randomized to either arm) will undergo handling sampling at enrollment (prior to randomization) and at two time points during their first study visit (see Figure below). At enrollment, we will sample both hands. During the first study visit, both hands will be sampled pre-visit (dog or control). Then the child will receive either the therapy dog session (including hand sanitizing) or a period of usual care. Study staff will then sample both hands again.

Study staff will ask the patient (or parent/legal guardian) when the child last bathed and when they last washed their hands.

Each hand sampling will be performed as follows: The patient will don a sterile latex-free examination glove and hand sampling solution will be instilled in the glove. The hand sampling solution will contain phosphate buffered saline and Tween 80 (a mild detergent). Study staff will gently massage the patient's hand within the glove for one minute. The hand sampling solution will transferred from the glove to a sterile specimen container and transported to the laboratory.



Laboratory studies
The overall cultivable microbial levels on patients' hands will be measured. In addition, testing for pathogens identified as organisms of concern will be performed using standard laboratory procedures.[19] These organisms include: *Staphylococcus aureus* (further evaluated for methicillin-resistance)
Vancomycin-resistant enterococci
Malassezia,
Aspergillus
Pasteurella
*Enterobacteriaceae (*further assessed for multidrug resistance)

Acinetobacter (further assessed for multidrug resistance)
Pseudomonas aeruginosa (further assessed for multidrug resistance) *Clostridium difficile*

Staff performing the laboratory studies will be blinded to the study ID (they will receive specimen IDs only), intervention assignment, visit number, and sampling time point (pre vs post). Laboratory studies will be performed at SCH using standard clinical microbiology laboratory criteria. More detailed laboratory procedures for laboratory staff are available in the laboratory protocol.

Clinical data collection
Study staff at SCH will review the patient's medical record to abstract basic patient demographics, cancer diagnosis, dates of hospitalization, dates and types of any infections that occurred during the study period (enrollment through 1 month post completion of participation), any antibiotics or antifungals received during the study period, and psychosocial care received during the study period. Review of study period data will be performed by a member of the SCH study staff who is blinded to the intervention status of the patient.

For parents/legal guardians enrolled in Phase 2, we will only collect the sex of the parent/legal guardian.

Discharge survey
The discharge survey includes the instruments outlined in the psychological assessment section above.

SCH study staff will administer to the patient and parent/legal guardian the day of or the day before anticipated discharge, or as close to that as possible. These surveys will be completed by the patient and parent/legal guardian on paper forms.

Follow-up surveys
Follow-up surveys include the instruments outlined in the psychological assessment section above.

At enrollment, parents/legal guardians, and the child when appropriate, will be asked to provide their preferred method for receiving the follow-up surveys (paper survey sent via mail or a link to the survey sent via email).

Patient and parent/legal guardian follow-up surveys will be sent to the parent/legal guardian/patient approximately 2-3 days after their first hospital discharge using the method preferred by the parent/legal guardian and/or patient as appropriate. Surveys will be sent by SCH staff.

A second follow-up survey will be sent 9 weeks after the first hospital discharge.

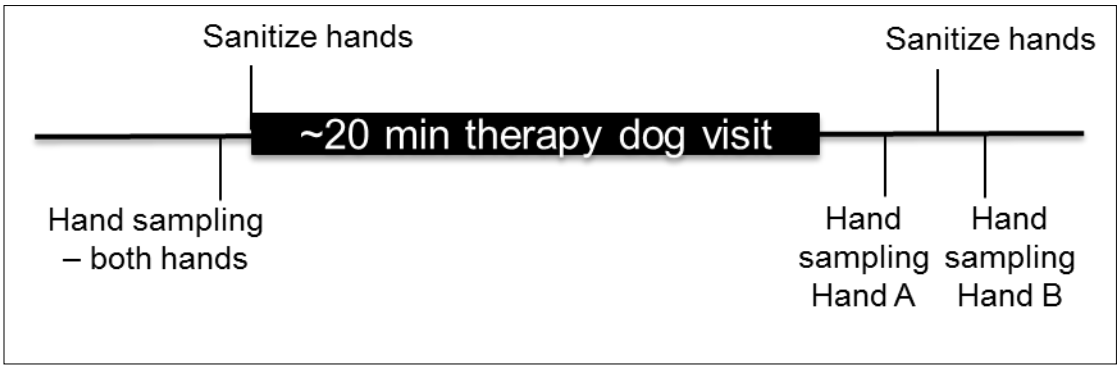
If no response to the follow-up survey is received with 5 days, a reminder email and survey link will be sent to parent/legal guardian or patients who prefer emailed surveys; parents/legal guardians or patients who prefer paper surveys will receive a reminder phone call from SCH study staff. If still no response has been received within an additional 5 days, paper surveys will be mailed to all parents/legal guardians and patients with a self-address stamped envelope regardless of their preferred communication method.

Procedures for Phase 3

Phase 3 is an observational study which involves a one-time therapy dog visit. Children will be instructed to touch the dog with both hands.

Both hands will be sampled before the visit. A randomly selected hand will be sampled immediately after the visit (before hand sanitization). The other hand will be sampled after sanitization.

The hand sampling method and laboratory assays will be conducted as described for Phase 2.



Study staff will ask the patient (or parent/legal guardian) when the child last bathed, when they last washed their hands, and which is the patient's dominant hand. Study staff at SCH will review the patient's medical record to abstract basic patient demographics, cancer diagnosis, dates of hospitalization, dates and types of any infections, and antibiotics or antifungals received in the 7 days prior to enrollment. Study staff will record which hand or hands touched the dog during the visit.

10.0 Data and Specimen Banking

Specimens will not be banked for this protocol. All study data will be managed using REDCap (maintained by ITHS at the University of Washington). Only members of the study teams at SCH and Kaiser Permanente Washington Health Research Institute (KPWHRI) will have access to the datasets within REDCap; however, only members of the study team at SCH will have access to direct identifiers. All analytic datasets exported from REDCap will be maintained by KPWHRI and will be maintained indefinitely. There is no plan to remove indirect identifiers (i.e., dates) from the dataset. Any proposals to use the data from an investigator outside the study team will be reviewed by Drs. Chubak and Zerr. If the data are to be used for a new research study, either by the study team or a new qualified investigator, Drs. Chubak at KPWHRI (study PI) and Dr. Zerr (site PI) at SCH would ensure IRB approval for the new research. As Dr. Chubak is the study PI and data will be held at KPWHRI, KPWHRI will be

responsible for releasing data and securing additional appropriate approvals such as data use agreements. SCH will not release study data.

No results from future research using banked data will be shared with research participants.

11.0 Data Analysis/Management

This section is applicable to Phases 2 and 3 only.

Analysis plan for Phase 2

All data collected will be screened for outliers and nonsensical values. Descriptive statistics and graphic procedures will be used to inspect distributions to ensure that they meet assumptions of statistical tests and estimation procedures. Descriptive statistics will be used to compare baseline covariates between intervention and usual care groups.

Aim 1: To assess the effect of therapy dog visits on psychosocial outcomes and satisfaction with care among pediatric oncology inpatients.

Our primary analysis will use an intent-to-treat approach: i.e., individuals will be analyzed by randomized group regardless of participation in any therapy dog visits.

Primary outcome: We will compare distress immediately following the first therapy dog visit in patients randomized to the intervention group with distress immediately following the first control period in patients randomized to usual care. Distress will be measured using the PedsQL Present Functioning Scales total score. We plan to plan to fit a linear regression model that regresses distress on an indicator for assigned treatment group adjusted for a parsimonious list of pre-specified baseline covariates.

Secondary analyses will be conducted for each of the individual scales on the PedsQL Present Functioning Scales (i.e., fear, sadness, anger, worry, fatigue, and pain) and for the emotional distress summary score, using the same approach as for the primary outcome.

Additional secondary analyses will compare discharge and follow-up survey items using generalized linear models adjusted for the same covariates as the primary outcome.

Outcomes will be modeled using the appropriate distributions and link function (e.g., binary outcomes will be modeled using binomial regression with logit link).

In exploratory analyses, we will look at differences in pre- vs. post-visit survey responses. We also plan to explore differences in the intervention effect by patient characteristics.

We will conduct per-protocol analyses as sensitivity analyses.

Aim 2: To determine whether therapy dog visits increase microbial levels on children's hands.

Both intent-to-treat and per protocol analyses will be conducted. We plan to reject the null-hypothesis of non-inferiority if the intervention of dog therapy visits is found to be non-inferior under both analyses.

Primary outcome: We will inspect the distribution of the microbial load outcome and apply transformations as needed (e.g., log10 as is common in the literature[20-22]) to achieve approximate normality. For the intent-to-treat analysis, we will compare total microbial levels immediately following the first visit in patients randomized to the intervention group to total microbial levels immediately following the first control period in patients randomized to usual care. For the per-protocol analysis, we will compare microbial levels immediately following the first visit in patients who receive a dog visit to microbial levels immediately following the first visit controls who would have been medically eligible for a visit. We will adjust for the value of outcome measured prerandomization (baseline), as well as baseline covariates. We hypothesize that, after hand cleaning following therapy dog visits, microbial levels on intervention patients' hands will not be meaningfully different than levels for usual care patients. We will apply a non-inferiority test, where our null hypothesis is that average microbial load in the intervention group exceeds that of the usual care group by pre-specified margin Δ, chosen to reflect a maximal "acceptable" difference. Levels of acceptable microbial load following hand cleaning in a pediatric inpatient population have not been characterized in the literature. Therefore, we plan to set Δ to be one SD of the outcome value at baseline (pre-randomization). We will apply a 1-sided test with an alpha-level of 0.025 (i.e., we will reject the null hypothesis if the upper limit of the 2-sided 95% confidence interval for the coefficient on the group indicator (intervention versus control) from the linear regression model is smaller than Δ). Analyses conducted at the hand-level will account for correlation of repeated measures from the same patient using generalized estimating equations (GEE) clustered at the patient.

We will also compare groups for the presence of organisms considered clinically important (Section 9.0).

In exploratory analyses, we will look at differences in pre- vs. post-visit microbial levels. We will conduct exploratory analyses as described above for Aim 1 (e.g., effect modification) and additional per-protocol analyses (e.g., hands that touched the dog vs. control patient hands).

Handling of missing data
We will evaluate if any covariates are associated with missing outcome information. As a sensitivity analysis, we will include any baseline predictors of missing outcome

information as covariates in our regression model to remove measured bias due to loss to follow-up.[23] If loss-to-follow-up is high, or if we find that post-baseline covariates significantly predict missing outcome information, we will consider using multiple imputation methods to increase our statistical power and further reduce bias.[23]

Analysis plan for Phase 3

Using data from Phase 3, we will estimate the difference between pre-visit microbial levels and levels following the therapy dog visit both before (post 1) and after (post 2) hand sanitizing. We will also compare post 1 and post 2 to each other and look for the presence of clinically important pathogens. In secondary analyses, we will stratify analyses by patient characteristics.

Power calculations

Aim 1

We estimated that we will have ≥80% power to detect an absolute mean difference between groups in our primary outcome of 13.0 (a difference smaller than the change observed in our pilot data). Our calculations[24-26] were based on a planned sample size of 40 patients (20 in each group) and a type 1 error rate (two-sided) of 0.05 and assume normally distributed outcomes with SDs equal to those for the pre-visit scores in our pilot study.

Aim 2

We calculated the minimal detectable non-inferiority margin (Δ) for testing the difference in mean bacterial load between the intervention and usual care groups for a fixed power of 80% and a 1-sided alpha level of 0.025.[27,28] Our calculations were based on a planned sample size of 40 patients (20 in each group). We assumed normally distributed outcomes with a common SD in the two groups, ranging from 0.5 to 1.4 log10 cfu/mL based on the published literature on hand cleaning methods in non-pediatric populations,[20-22] assuming no difference in means between groups. Based on these calculations, we will have ≥80% power to detect non-inferiority with a margin of Δ=0.4 log10 cfu/mL when 2the SD is 0.5 and a margin of Δ=1.3 log10 cfu/mL when the SD is 1.4.

12.0 Confidentiality

Procedures at SCH

Study data collected on paper forms (such as completed patient surveys) will be stored in locked cabinets. Paper forms will not include direct identifiers. As stated in section 10, all study data will be managed using REDCap. Data recorded on paper forms (e.g. survey responses) will be entered by KPWHRI staff and clinical data will be entered by SCH staff. Access to the REDCap databases will only be given to members of the research team upon protocol training and any IRB approval to add them to the study

team (if a new member). Likewise, access will be removed from an individual if they are no longer a member of the team.

A tracking database of all patients admitted to the Cancer Care Unit during the enrollment period will be maintained. This database will include direct identifiers (see rationale in section 29) as well as an assigned screening ID. This database will be accessible only by SCH study staff (a dataset identified by screening ID only will be viewable/exportable by KPWHRI).

Datasets containing study visit, clinical, and laboratory data will not include direct identifiers and will be identified by study ID and/or specimen/survey ID only.

Medical record data abstraction will be performed by SCH study staff; KPWHRI staff will not review medical records.

Specimens will not contain direct identifiers (specimen ID only). Specimens will not be retained for this study and specimens will not be sent to KPWHRI.

Procedures at KPWHRI
Study data collected on paper forms will be stored in locked cabinets and electronic data will be maintained in secure databases and files accessible only by study staff. Dr. Chubak and Ms. Hawkes will control access within KPWHRI.

Data transfers from SCH to KPWHRI
Data on paper forms (e.g. patient surveys) will be hand-delivered by a member of the SCH research staff to the appropriate staff at KPWHRI. KPWHRI is in close proximity to Seattle Children's Research Institute (where Ms. Adler's office is located). Electronic health record data will be entered directly by SCH staff into study databased managed in REDCap. Both SCH and KPWHRI study teams will have access to the REDCap databases; electronic data transfer is not anticipated. KPWHRI will export limited datasets for analyses and these analytic datasets will be stored on a secure KPWHRI server. The limited datasets exported by KPWHRI will not include direct identifiers but will include indirect identifiers (such as dates). Direct identifiers (names, contact information, etc.) will be shared with KPWHRI investigators if needed to investigate adverse events.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

We will collect data on any adverse events that occur from enrollment to 1 month post study participation completion.

Definitions

For this study, **adverse events** are injuries, allergic reactions, or breach of confidentiality that are possibly, probably, or definitely related to (a) the interventions and interactions used in the research, OR (b) the collection of identifiable private information for the research.

Serious adverse events are defined as any event that is possibly, probably, or definitely related to the research (occurring at any dose or level of the intervention) that results in any of the following:

- Death
- Life-threatening event
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity; OR any event judged by a medical professional to jeopardize the health or well-being of the participant and may require medical or surgical intervention to prevent an outcome listed in this definition.

Sources of adverse event data

Adverse events and unanticipated problems could come from the following sources:

- The patient's clinical team
- Direct observation from study staff during study visit/intervention
- Parent/legal guardian report either reported directly to the study team or reported on a survey
- Patient report either reported directly to the study team or reported on a survey
- Documentation in the medical record upon retrospective 1-month postcompletion review

Reporting adverse events

The study manager at SCH will report any adverse events, other than patient death, to Dr. Zerr (site PI), Dr. Chubak (study PI), and the study manager at KPWHRI within 2 business days and complete an adverse event form. All adverse event forms will be reviewed weekly and forwarded to the study's medical monitor for review, determination of attribution, and a recommended course of action if applicable. The IRB will be notified within 5 business days of discovery of the event.

The study manager at SCH will immediately report any patient death to Dr. Zerr (site PI), Dr. Chubak (study PI), and the study manager at KPWHRI. An adverse event form will be completed immediately and forwarded to the medical monitor for review, determination of attribution, and a recommended course of action if applicable. While extremely unlikely, the IRB will be notified of any deaths deemed possibly, probably, or definitely related to the study within 24 hours of the medical monitor's review.

Reporting schedule to IRB	Report Within 1 Business Day of Medical Monitor Review	Report within 5 Business Days of Discovery	Summarize at Continuing Review
Unexpected death of research participant that is at least possibly related to the study.	⮝		⮝
Other serious adverse events		⮝	⮝
Other adverse events		⮝	⮝
DSMB reports with findings that suggest action is necessary or that under enrollment will cause data validity issues; discovery of increased frequency and/or severity of adverse events; or discovery of an unanticipated problem(s).		⮝	⮝

DSMB

We will establish a Data Safety Monitoring Board (DSMB). The DSMB will consist of a pediatric oncologist, a biostatistician, an infectious disease specialist, and a microbiologist. A monitoring plan will be established prior to the start of recruitment. Once recruitment commences, the DSMB will review adverse event data and infections between the two study groups when data collection is complete for half of the patient (n=20) and again when data collection is complete for all patients in Phase 2. DSMB findings will be reported to the IRB and the National Institute of Child Health and Human Development (NICHD) at the NIH.

Suspension of the protocol

Although we do not anticipate any differences in infections between groups, deaths or serious adverse events at least possibly related to the study, if any were to occur, we would stop the trial and seek guidance from the DSMB, IRB, and the NICHD before resuming the trial.

14.0 Withdrawal of Subjects

There are no anticipated circumstances under which participants will be withdrawn from the study without their consent. However, there are circumstances involving patient safety that could result in permanently stopping the therapy dog intervention during Phase 2. This includes circumstances such as discovery or development of allergy to the dog despite efforts to screen for dog allergies. Or, the patient may experience a change in their medical condition that leads the patient's oncologist or parent/legal guardian to decide it is in their best interest to discontinue the intervention.

There may be circumstances where the intervention will need to be withheld temporarily (such as the patient has been placed in isolation). This does not constitute withdrawal from the study. The intervention will resume once it is appropriate (e.g. patient was removed from isolation).

Participants may refuse participation at individual data collection points or the intervention on a given day without withdrawing from the study. Patients who refuse the intervention/usual care period on their first visit will still be asked to complete hand sampling and surveys at that visit.

If a patient or parent/legal guardian requests to permanently withdraw from the study, no additional data will be collected, but we will retain any data collected up to the point of withdrawal.

We will record reasons for withholding the intervention, intervention refusal, data collection refusal, and study withdrawal.

15.0 Risks to Subjects

Risks associated with surveys
Patients and parent/legal guardians may experience discomfort at answering questions on the surveys. Patients and parent/legal guardians will be told they can skip any question that makes them feel uncomfortable. Most of the instruments in this study have been used in many pediatric studies therefore we expect discomfort to be rare, limited in magnitude, and short in duration.

Risks associated with hand sampling
Patients might feel uncomfortable during hand sampling (the procedure tickles, etc.). We expect this to be minimal since the hand sampling procedure is brief. Further, we will optimize our hand sampling method in Phase 1 to minimize any discomfort. There is also a small risk a patient will have a skin reaction to the hand sampling liquid. We expect this to be rare as the hand sampling liquid consists of saline and a very small amount of detergent. This solution has been used in many studies. We expect any discomfort with the hand sampling procedure to be rare, limited in magnitude, and short in duration.

Risks associated with the intervention
Possible risks associated with the therapy dogs include injury, allergy, and infection. However, the therapy dogs used in this study are those that are part of the Therapy Dog program at SCH and have undergone screening and have successfully visited SCH patients before; therefore, we expect the risk of injury to be extremely low. There is a small possibility that patients could develop an allergic reaction to the dog despite our best effort to exclude patients with dog allergy. Further, there is a possibility that a patient could contract a pathogen from the dog. We anticipate this risk to be very low as patients will be instructed to clear their hands following interaction with the dog. To our knowledge, no prior studies of therapy dog visits have reported the outcomes listed above; therefore, we anticipate these risks to be rare.

In Phase 2, patients who are randomized to the usual care arm (no therapy dog visit) may feel disappointed at not getting a visit from a therapy dog. We will make every effort to ensure patients and parent/legal guardians understand there is a 50/50 chance they will not have a visit from a therapy dog. We expect this risk to be relatively common but limited in magnitude and short in duration, as therapy dogs are currently not allowed on the unit.

Risks associated with confidentiality
There is a minimal risk of breach of confidentiality. This risk is minimal because we have multiple safeguards in place (see section 12) to ensure confidentially is protected.

Risks to others not participating on the trial
There is a possibility that patients not participating in this trial could interact with a therapy dog incidentally, such as in the hallway. This risk will be minimal as the therapy dog teams will be instructed to interact only with persons who are enrolled in their study during study visits that occur in enrolled patients' rooms.

There is also a possibility that the visitors or other family members of a patient participating in this trial (and randomized to the intervention arm) could interact with the dog while the study visit is occurring in the patient's hospital room and would therefore be subject to the same risks as patients participating in the study. Risks will be minimized by requesting anyone who touches the dog clean their hands before and after contact, consistent with SCH policy.

Patients who are not enrolled in this trial may experience disappointment because they do not get to interact with a therapy dog.

16.0 Potential Benefits to Subjects

Children enrolled in Phase 1 of the study are not expected to benefit from this study.

Children in the intervention arm of Phase 2 may experience less distress, including decreases in worry, tiredness, fear, sadness, and pain. Based on our pilot data, these potential benefits are likely but may vary in magnitude.

Parent/legal guardians of children in the intervention arm of Phase 2 may experience positive emotions if their child's distress is reduced. These potential benefits may also vary in magnitude.

Children enrolled in the control arm of Phase 2 and their parent/legal guardians are not expected to benefit from this study.

Children enrolled in Phase 3 may experience less distress, including decreases in worry, tiredness, fear, sadness, and pain.

17.0 Vulnerable Populations

We will not enroll neonates, prisoners, cognitively impaired adults, or wards of the state. Mothers or other female legal guardians patients who enroll in this study may also participate, and some may be pregnant during their participation. Participation of parent/legal guardians in Phase 2 is limited to completing surveys; therefore, this study poses no risk to the pregnancy.

This study includes children aged 5-17 years. This study involves no more than minimal risk and appropriate provisions for soliciting parent/legal guardian consent and patient assent will be performed as described elsewhere in section 29.

18.0 Community-Based Participatory Research

N/A.

19.0 Sharing of Results with Subjects

Patients and their parent/legal guardians enrolled in Phases 2 and 3 will be asked at enrollment if they would like to receive a copy of study manuscripts. We will also distribute the resulting manuscript(s) to our colleagues in oncology. All data in the resulting manuscript(s) will be in summary form only. We will not disclose individual trial results to participants, their families, their providers, or anyone else.

20.0 Setting

This study represents a partnership between Kaiser Permanente Washington Health Research Institute (KPWHRI, formerly Group Health Research Institute) and Seattle Children's Hospital (SCH). The protocol and study materials will be developed collaboratively at both institutions.

Patients will be identified and recruited at SCH by SCH staff. All research procedures outlined in section 9 of the protocol will be performed at SCH by SCH staff.

Randomization will be performed by KPWHRI. Study databases will be maintained by KPWHRI and data analyses will be performed by KPWHRI staff. SCH will serve as the IRB of record for research activities. An Institutional Review Board Authorization Agreement will be completed between the two institutions.

21.0 Resources Available

The study teams at both institutions (SCH and KPWHRI) have extensive research experience in the proposed study population.

Danielle Zerr, MD, MPH, the site PI at SCH, is the Chief of Infectious Diseases at the University of Washington and the Medical Director of the Infection Prevention Program at SCH. She has extensive experience conducting infection prevention-related research as well as research with this patient population. The research coordinator for this project has 18 years of experience coordinating Dr. Zerr's studies at SCH. Dr. Xuan Qin, director of the clinical microbiology lab at SCH, will oversee the laboratory studies.

Jessica Chubak, PhD, the study PI, is a cancer epidemiologist with experience conducting animal assisted activity studies including the pilot study at SCH. The research coordinator at KPWHRI also has 18 years of experience coordinating research studies including the pilot study that was performed at SCH. Evette Ludman, PhD, coinvestigator at KPWHRI, is a clinical and behavioral psychologist. She has extensive experience in the development and evaluation of innovative behavioral health and chronic disease self-management interventions. The team at KPWHRI includes biostatisticians and data programmers to manage the data held at KPWHRI and perform the data analyses outlined in this protocol.

We do not anticipate enrolling more than 80 patients (10 in Phase 1 and up to 50 in Phase 2 [and a similar number of Phase 2 parents/legal guardians] and up to 20 in Phase 3) from the population of patients hospitalized on the Cancer Care Unit over the 12-month enrollment period. We have sufficient staff to support this project.

SCH's Therapy Dog Program resides with the Child Life Department. Currently, there are 10 dog/handler teams who visit patients throughout the hospital. This team has sufficient resources to support this project.

KPWHRI is the public-interest research arm of Kaiser Permanente Washington (formerly Group Health). This Institute was established to improve healthcare through high-quality research and dissemination of results into the public-domain. KPWHRI has sufficient resources to support their work on this project.

22.0 Prior Approvals

The study was reviewed by the funder, the National Institutes of Health. The Infection Prevention Program at SCH has approved the study. Please note the local PI of the project is the Medical Director of the Infection Prevention Program at SCH.

The protocol has also been reviewed by Cancer Care Unit Leadership and Child Life Department/Therapy Dog Program leadership.

After consultation with the IACUC within the SCH Office of Institutional Assurances, it was determined this protocol did not require IACUC review.

23.0 Recruitment Methods

Patients will be recruited while they are inpatients in the Cancer Care Unit at SCH.

Potential participants will be identified through medical record review and approached by study staff in their hospital room. A member of the patient's clinical team will first ask the patient/family if they agree to let a member of the study staff approach them about the study. No materials will be used for recruitment.

Patients (children) who enroll in Phase 1 of the study will receive a one-time $10 check once the hand sampling has been performed.

Patients (children) who enroll in Phase 2 of the study will receive a $15 check upon completion of the first follow-up survey and an additional $20 check once the final survey is collected. Parent/legal guardians who enroll in Phase 2 of the study will receive $15 upon completion of the first follow-up survey and an additional $20 check once the final survey is collected.

Patients who enroll in Phase 3 of the study will not receive an incentive since they will all receive a therapy dog visit.

24.0 Use of Social Media

N/A. Social media will not be used for this study.

25.0 Local Number of Subjects

We will enroll 10 patients into Phase 1 and up to 50 patients into Phase 2. We anticipate recruiting up to 50 parent/legal guardians in Phase 2. We plan to enroll up to 20 patients in Phase 3.

26.0 Provisions to Protect the Privacy Interests of Subjects

All data will be stored in password-protected databases and folders on secure servers and password-protected computers. Paper forms will be kept in locked cabinets in

secure offices. Participants will be informed of the methods used to protect their privacy and the consent form will clearly state who will have access to their information.

We will clearly explain the voluntary nature of the research and that participants may decide to stop at any time and that they can refuse or skip any question or procedure that makes them ill-at-ease. The study team at SCH has many years of experience interacting with this population. Also, we are using age-appropriate instruments and will be using an optimized method for hand sampling based on feedback from the population enrolled in Phase 1.

Data will be stored securely and no direct identifiers will be included in analytic files. Only appropriate study team members will have access to data. More detail is outlined in section 12.

27.0 Compensation for Research-Related Injury

This study involves no more than minimal risk. There is a very small risk of a participant being bitten by the therapy dog although this has never been reported. It is also possible that a patient could have an allergic reaction to the dog despite our effort to exclude patients who are allergic to dogs. If either of these events occur, the patient or their insurance company would be responsible for these charges.

Any injury to an individual not participating in this study (e.g. a visiting family member), that is the direct result of interacting with a therapy dog (such as an injury) will be evaluated following the Child Life/Dog Therapy Program standard policies and procedures.

28.0 Economic Burden to Subjects

There are no anticipated costs to patients or their families. All patients will be hospitalized at SCH during the study period. There are no costs associated with the therapy dog visits as the dog therapy teams at SCH are staffed by volunteers. The 3-day post-discharge follow-up and 9 week post-discharge visits will occur via web- or mailbased survey. Patients/families do not need to return to SCH for follow-up.

29.0 Consent Process

Informed written consent and assent (when appropriate) will be obtained by study staff at SCH. Consent conferences will be performed in the patient's hospital room (all rooms on the Cancer Care Unit are private rooms). The study team member will provide a full explanation of the research including all procedures the voluntary nature of the research. The consent process will follow the SCH standard operating procedure (HRP-090).

Non-English Speaking Subjects

Non-English speaking patients are not eligible to participate in this research. The primary outcome depends upon patient responses to validated instruments. Unfortunately, not all of the instruments used in this study have been validated for non-English languages.

Waiver of Consent and HIPAA

We will seek a partial waiver of HIPAA authorization for screening/recruitment purposes. We will review medical records to screen patients for eligibility. Recruitment information will be maintained in a secure tracking database. This information will contain direct identifiers. Some patients may initially be ineligible but become eligible at a later date (such as removal from isolation). Tracking is also needed to ensure patients who have already been deemed ineligible for reasons that will not change (e.g., allergy to dogs) or have permanently refused to not have their medical records review unnecessarily. We will also track reasons why patients refuse or are ineligible for the study. Individual-level tracking information will not be shared outside the study team; however, we will report summary data on reasons for refusal and ineligibility. All direct identifiers on patients not enrolled in the study will be destroyed as soon as enrollment has concluded and this information will not be reused for any purpose. The waiver is necessary to determine eligibility and track eligible patients to ensure we meet our enrollment goals and understand the generalizability of our study population. Recruitment could not practicably be carried out without this waiver as the necessary eligibility information is found in the patient's medical records. Direct identifiers are needed for accurate tracking for the reasons above.

We will seek a waiver of consent for participants who turn 18 but with whom we are no longer interacting. We do not plan to have further contact with patients once participation is complete and will not be contacting patients for additional data. Dates are the only identifier retained in the analytic dataset. These dates are needed to assess temporality of outcomes. Further, we believe that contacting participations who reach the age of majority after their participation is complete would pose a greater risk of privacy intrusion than the minimal risk of breach of confidentiality associated with the research procedures once the patient has completed participation. We also believe we need this waiver as we may not have updated contact information on patients once they are adults.

Patients who are not yet adults (infants, children, teenagers)

For this study, all patients will be aged 5-17 years at the time of enrollment and will be considered to have not reached the age of majority. Consent will be obtained only from a parent/legal guardian or the patient's legal guardian (we will not enroll wards of the state). We will consult the information in EPIC to confirm the status of the individual providing consent. For the child to participate in the study, we will seek consent from one parent/legal guardian as this study is no more than minimal risk and is not a treatment trial. Participation in the parent/legal guardian portion of Phase 2 will be offered to one parent/legal guardians if applicable.

Written assent will be obtained from patients aged 7-17 using the appropriate assent form. Children younger than 7 will still be asked for verbal assent since it is important for them to be comfortable with the procedures (e.g., hand sampling).

Since patients enrolled in Phase 2 of the study may receive the study intervention (therapy dog visit or control) during each hospitalization that occurs during the study period, we will re-consent any patient who reaches the age of majority while the study procedures are still occurring. We will request a waiver to re-consent patients who reach the age of majority once we are no longer interacting with patients but data analysis of identifiable information is ongoing as described above.

Cognitively Impaired Adults
We will not enroll cognitively impaired adults. All adults enrolled in this study will be parent/legal guardians of children enrolled in Phase 2 therefore we do not expect parent/legal guardians to be cognitively impaired. However, if we have any concerns about the consent capacity of a parent/legal guardian we will discuss our concerns with the members of the clinical team such as the social worker.

Adults Unable to Consent
All adults enrolled in this study will be able to provide consent.

30.0 Process to Document Consent in Writing

Documentation of written consent will be performed by following the SCH standard procedure outlined in HRP-091.

31.0 Drugs or Devices

N/A. This study does not involve drugs or devices.

32.0 Good Clinical Practice

We have committed to conduct the described study per International Center for Harmonization of Good Clinical Practice (ICH-GCP).

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