Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: Video Images about Decisions for Ethical Outcomes in Pediatrics (VIDEO-PEDS)

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1. Summary

Background: Cancer remains the leading cause of death in children.[1] Parents of children with cancer often face complicated decision making throughout their child's illness. The National Academies of Sciences, Engineering and Medicine have called for the development of interventions to increase effective goals-of-care (GOC) communication.[2] GOC interventions help patients, their families, and clinicians communicate and discuss preferences for treatments together to ensure medical care is "consistent with the family's values, goals, and informed preferences."[3,4] To date, most GOC interventions have focused on adults and adolescents resulting in a critical disparity of available tools for children with advanced cancer. While most studies show better family outcomes when parents are prepared for the child's end of life,[5-7] GOC conversations are grossly inadequate. Specifically, GOC conversations between parents, who serve as primary decision makers for children, and clinicians often rely on verbal or written information about possible medical interventions, such as cardiopulmonary resuscitation (CPR) or placement on a respirator, during crises of clinical decline.[4] However, this approach is often inadequate as it is presently conducted, leaving families ill-prepared in times of distress.[8]

The majority of children with cancer and their families prefer to die at home, yet most children with cancer die in the hospital, and this disproportionately affects African American, Hispanic, and rural patients.[9-13] Novel interventions are needed to ensure GOC conversations happen earlier to ensure goal-concordant care.[14] The lack of GOC discussions may be due to clinician reliance on *ad hoc* verbal descriptions of goals and possible treatment options. Treatment options (e.g., CPR) are difficult for parents to envision. Moreover, the information provided is often variable, and verbal explanations of medical interventions are less effectual given literacy and language barriers.[15-17] To address these shortcomings, we have developed theory-based GOC video decision aids in English and Spanish for patients with cancer.[18-32] We have shown the efficacy of similar decision aids in adults using Natural Language Processing (NLP), a form of computer-assisted abstraction, in pragmatic trials; but have not examined the impact of these videos in children with cancer and their parents.

Aims: The overall objective of this UG3/UH3 study is to build the infrastructure for and conduct a large randomized pragmatic trial in three diverse health care systems (Dana-Farber Cancer Institute, Children's Healthcare of Atlanta, and the University of Alabama).

UG3 Aims (Establish a trial infrastructure in three health care systems)
Aim 1: Guided by patient and clinician input, refine and finalize the GOC Video Intervention.
Aim 2: Finalize clinics and workflows to implement the intervention.
Aim 3: Validate and fully define clinically meaningful NLP outcome measures.
Aim 4: Pilot-test the intervention and outcomes in 9 patients with cancer at each site to ensure feasibility.

UH3 Aims (Conduct a large pragmatic randomized waitlist-controlled trial)
Aim 1: To compare GOC documentation in 504 patients aged 0-12 with cancer randomly assigned to our GOC Video Intervention vs. Waitlist-Control. ***Hypothesis (H) 1a:*** *Intervention patients will be more likely to have GOC documentation compared to Waitlist-Controls during the intervention period.* ***H1b:*** *Intervention effects will be greater in African American, Hispanic, and rural patients as compared to non-Hispanic, non-rural Whites.*
Aim 2: To characterize detailed patient- and parent-centered outcomes. ***H2****: Patients and parents in the intervention phase (vs. control) will have improved outcomes.*

Aim 3: Using the RE-AIM QuEST mixed-methods framework, we will assess dimensions critical for consistent use, implementation, and adoption of the program in clinical settings using mixed methods.

Methods: The study will be conducted in phases. 1) Recruitment for focus groups to inform development of the video decision aid. 2) Refilming of video decision aid, training navigators. 3) Pilot-test the intervention and surveys in 9 children with cancer and their parents at each site: This will involve 9 parents per site (one per child) from 3 enrolling sites (27 total), who will all receive the intervention. Our goal will be to ensure that the intervention is appropriate as well as useful to parents and the clinical staff before we conduct the larger pragmatic trial.

Randomized, waitlist-controlled trial (RWCT): Following the finalization of the video decision aid, we will conduct a large, pragmatic, randomized, waitlist-controlled trial (RWCT) including 504 parents of children with cancer aged 0-12 years. This trial will target parents of 76 African American, 76 Hispanic, and 76 rural children with cancer (45% of total enrollment) by design. Parent participants will be randomized to Waitlist-Control or the GOC Video Intervention in which the video decision aid will be shared with their parents along with in-person and telehealth sessions conducted by Navigators to elucidate GOC preferences. After the intervention period (detailed below), the waitlist will open and all parents (i.e., Waitlist-Controls) will receive the intervention. Using NLP to detect outcomes (e.g., GOC documentation), we hypothesize that children of parents that receive the intervention, as compared to controls, will have more GOC documentation (primary outcome).

Timeline and random assignment: We will conduct three cycles of the nine-month RWCT design as shown in Figure 5. Thus, over the course of 27 months, three cycles of unique participants will be randomized (9 months per cycle x 3 cycles = 27 months). The recruitment period is 36 months to account for the last nine months of intervention for Waitlist-Controls in the last cycle. We will examine data on a total of 504 children with cancer and their parents over the course of the four years of the UH3 Phase. At the start of each our three cycles, we will ask each health system to curate and finalize a list of all eligible patients. For each cycle, one-third of the total 504 participants (i.e., N=168) will be randomized in 1:1 assignment, stratified by health system and demographic characteristic (African American, Hispanic, and rural) to Waitlist-Control or GOC Video Intervention. For each cycle, there will be pre-specified subgroups targeting parents of 25 African American (15%), 25 Hispanic (15%), and 25 rural children (15%). (Please note that 76 per subgroup over the course of three years ÷ three cycles ≈25 patients per subgroup per cycle, a very reasonable goal).

Race/ethnicity variables are based on the commonly used methods of self-identification within the EHR, and our three health care systems are within national guidelines for reliable race and ethnicity data.[162] Race/ethnicity will be of the child; thus, parents may be a different race. Rural will be defined using the U.S. Census method.[163] Within the rural subgroup, we will aim to include by design 15% (N=11) African American rural children and 15% (N=11) Hispanic rural children. In 2021, 24% (105 children) of rural children were African American and 18% (75 children) of rural children were Hispanic, making the proposed recruitment numbers for rural African American and rural Hispanic children high feasible. At the start of each of our three cycles, a new list of eligible children with cancer will be curated since this will change over time (i.e., every nine months).

Outcomes: In the development and pilot phase (UG3), outcomes of acceptability and usefulness will be defined by parent and clinician feedback gathered in the focus groups and survey data.

NLP outcome measures: For the proposed trial, we will use NLP, a form of computer-assisted abstraction, to detect primary and secondary outcomes (e.g., GOC documentation). Our research group has published the original studies using NLP in GOC research, as we have already successfully applied this methodology in other large-scale trials and have already validated the NLP for the pediatric cancer care context.[21,22,25-29,32,48,87,88,94,106-109,146] Below, we detail the software program we developed and annotator training. The ability to use NLP to rapidly abstract outcomes from a large number of EHR records lays the groundwork for the VIDEO-PEDS Proposal. A rule-based software equipped with text annotation capabilities will be used to assess outcomes for the study. This software, ClinicalRegex,[147] was developed by our research team. The software has been used to assess process-based quality measures in multiple studies across clinical settings.[110,112,148-160] ClincalRegex identifies all pre-specified keywords and phrases within a corpus of text (i.e., clinical notes). Human annotators then use ClinicalRegex's user interface and pre-specified annotation guidelines to interpret the documentation and to indicate whether the keywords and phrases identified by the software are in the appropriate context.

2. Background and Significance

2.1 Background

Mounting evidence suggests that children with cancer and their parents rarely participate in GOC discussions and receive intensive care at the end of life: Increasingly, adults and adolescents with cancer have access to interventions aimed at facilitating GOC discussions.[33,34] However, children and parents, their natural decision makers, typically experience *ad hoc* GOC discussions, driven primarily by individual clinicians and often too late during clinical crises.[5] As a likely result, young patients with cancer often receive intensive medical services at the end of life.[10] Specifically, children experience high rates of hospital deaths, intensive care unit admissions, and intubation and CPR.[3] Compared with adults, children are also more likely to receive cancer-directed therapy at the end of life.[2] Parents of children with cancer experience high levels of psychological distress[35] and when not well-supported in decision making, experience high levels of regret.[36] Parental grief is prolonged, intense, and is highly associated with the child's end-of-life experience. Importantly, our clinical experience and the literature suggest that parents of young children with cancer hold multiple, blended GOC, including hoping for life extension and child comfort. For example, parents may opt for continued cancer-directed therapy, yet wish to forgo care in the ICU. High-quality GOC discussions are required to delineate nuanced goals for medical care[2]; however, we are not aware of any formal GOC interventions for parents of young children with cancer. Notably, early GOC communication facilitates less intensive medical care among adults, including fewer high-intensity interventions, fewer terminal hospitalizations, earlier palliative care use, more hospice use, and better family bereavement outcomes.[2,37] GOC interventions are urgently needed among pediatric patients with cancer to ensure medical care is "consistent with the family's values, goals, and informed preferences."[3,4]

Ethical framework for decision making in pediatric patients vs. adults: In adults, substituted judgment (what decision would the patient have made if they were able to make decisions) is the common standard used for patients without capacity.38,39 In pediatric patients aged 0-12, this is an uncommon standard for decision making. Rather, clinicians and parents are expected to consider the child's "best interests"5 in decision-making. Best interests determinations, however, are complicated by variable clinician and parent values and priorities.[40] Parents are generally better situated than others to understand the unique needs of their children and to make appropriate, caring decisions regarding their children's healthcare.[38,39,41] As some have noted, this is not an absolute legal right because clinicians have an interest in protecting the

child from harm and can challenge parental authority in situations in which a minor is put at significant risk of harm.[38,39,41] Parental decision making is primarily understood as parents' responsibility to support the interests of the child and to preserve family relationships, rather than being focused on their rights to express their own autonomous choices.[41] Clinicians must balance the need to work collaboratively with parents, respecting their cultures, religions, and the importance of family autonomy with the need to protect the child from harm.[41] Informed GOC conversations facilitate better outcomes. However, as practiced today, most pediatric patients with cancer do not have GOC discussions documented in their medical records suggesting that shared decision making and parents' preferences, which are based on understanding the unique needs of their children, may be overlooked and lead to poor quality end-of-life care.[14]

African Americans, Hispanics, and people with low health literacy experience poor quality end-of-life care: African American and Hispanic children are disproportionately affected by poor end-of-life outcomes. Specifically, compared to white patients they are more likely to experience death in the hospital and hospice use is highly varied.10,42 Substantial communication disparities exist; for example, pediatric oncologists often underestimate the information needs of minority parents[43] and are inaccurate in predicting decisional preferences.[44] Language barriers also negatively impact the quality of informed decision making in pediatric cancer care.[45] Unfortunately, low health literacy and low English proficiency serve as significant communication barriers impeding high-quality GOC discussions.[46] Approximately 90 million U.S. adults have low health literacy and the prevalence of low health literacy is higher among minorities and people with low educational attainment.47 People with low health literacy are much more likely to misunderstand key facets of GOC discussions.[30,48] Similarly, people with low health literacy and/or low English proficiency are less likely to have GOC discussions, an advance directive, health care proxy, or to have discussed their medical wishes with their family members.[17,49-56] In addition, people with low health literacy are more likely to want intensive end-of-life care as their initial approach to care; however, we have shown that brief, balanced, video decision aids significantly improve knowledge, decisional certainty, and better align preferences for care with individual values among people with low health literacy.[30,57] Addressing the needs of these communities has the potential to improve the delivery of medical care.

GOC research in rural populations is urgently needed and has been understudied: The majority of GOC research has been conducted in metropolitan settings and populations.[3,58-60] This rural-urban divide in GOC studies is a glaring gap in the literature given the dearth of palliative care specialists in rural areas.61 In many health care contexts, it has been well-documented that rural populations have a heightened risk for poor quality of care.[61-64] Research focused on GOC in rural populations is urgently needed and offers the potential to improve the decision making and health care experience of Americans living in rural areas.

Video decision aids improve GOC discussions and health care delivery by surmounting health literacy and communication barriers: The traditional approach to GOC discussions, which primarily relies on ad hoc verbal descriptions of hypothetical clinical situations and treatment choices, is limited because complex scenarios are difficult to envision, provider information is inconsistent, and verbal explanations are hampered by literacy, emotional and language barriers.[2,65-67] This is particularly true for parents who are making decisions for ventilatory support or other life-prolonging interventions for their child.[68,69] Parents' heightened emotional state may interfere with cognitive processing and this reaction may be exacerbated when clinicians insufficiently attend to this affect and emotion.[70-74] For the GOC process to lead to optimal decisions, parents require accurate and comprehensible information about their options, and a care setting where communication needs are addressed early in the illness trajectory.[75-78]

Over the past few years, investigators have recognized the shortcomings of prior efforts and have developed new interventions to better facilitate GOC discussions and the delivery of better-aligned medical care with individual values. [2,79-84] The theory-based video decision aids proposed for this study focus not only on GOC-related decisions such as resuscitation preferences, but also provide education about palliative care and hospice services earlier in the course of serious illness. The videos attempt to overcome language and literacy barriers and to present potential scenarios with a sense of reality lacking in verbal descriptions.[28-30] These videos have been proven effective in adult patients in increasing GOC conversations, GOC documentation, and hospice utilization.[18-20,22,24,27,48,85,86] Increase in hospice utilization avoids unwanted burdensome interventions, better aligns patient preferences with care delivery, leads to improved caregiver bereavement, and results in more cost-effective care. [18-20,22,24,27-30,48,87.] The VIDEO-PEDS study proposed is based on strong evidence that communication barriers can be overcome with high-quality GOC discussions using video decision aids.

Optimizing GOC discussions with video decision aids and navigators: Navigators will be used to help parents of children with cancer use their knowledge of their child and family along with information obtained from video decision aids to contemplate GOC and future decision making. Navigators will be trained in VitalTalk, which is the most widely disseminated evidence-based teaching method that focuses on patient-centered communication skills training. [88-90] Prior work, including several RCTs, supports the efficacy of the GOC videos with navigators. [86,91-93] The VitalTalk model is built upon the premise that effective learning of communication skills requires observation of exemplar behaviors and observed practice with targeted feedback and includes training in skills related to GOC conversations and responding to emotion. The curriculum is delivered in an online format combining both synchronous and asynchronous components and continuing to apply state of the art learning principles. In earlier studies, VitalTalk demonstrated that trained participants acquired a mean of 5.4 new skills in delivering bad news ($P < 0.001$) and 4.4 new skills in GOC ($P < 0.001$).94 VitalTalk has over 500 faculty, has trained over 14,000 clinicians, runs courses around the world, and is in high demand by health care systems.

A pragmatic, randomized waitlist-controlled trial (RWCT) is well-suited to evaluate the implementation of the GOC Video Intervention: Pragmatic trials are increasingly used in health services research, and there are several notable advantages of this design for testing communication interventions.[95] A significant barrier to large trials is the challenge of individual enrollment. With the RWCT design, all patients will eventually receive the intervention and individual written consent procedures are waived, consistent with the low-risk nature of the intervention. The large number of patients also allows for robust subgroup analyses (i.e., African American, Hispanic, and rural patients). The RWCT design is ideally suited to evaluate implementation of communication interventions and conduct subgroup analyses.

Pragmatic trials evaluate GOC interventions under real-world clinical settings: To date, most randomized GOC trials evaluated the effects of interventions under ideal circumstances (i.e., explanatory trials).[96-99] Explanatory trials are often plagued by poor enrollment and predominantly white populations.[96-100] Based on the Pragmatic–Explanatory Continuum Indicator Summary Tool, the rationale for the proposed pragmatic trial is compelling. [101-105] Further evidence for the feasibility of this pragmatic trial include clinics and hospitals chosen that have efficient and established infrastructures for new program implementation as well as integrated electronic health records (EHRs), providing an easily accessible data source for patient phenotype characterization, intervention implementation, and outcomes measurement. Thus,

the proposed pragmatic trial is a logical next step towards understanding the real-world application of the intervention.

Natural Language Processing (NLP) allows for trials of this size: For the proposed trial, we will use NLP, a form of computer-assisted abstraction, to detect the primary outcome (GOC documentation). Our research group has published seminal studies using NLP as we have already successfully applied this methodology in other large-scale trials. [22,25,86,91,92,94,106-112] The ability to use NLP to rapidly and more efficiently abstract outcomes from a large number of EHR records lays the groundwork for a trial of this magnitude and complexity.

2.2 Preliminary work

Preliminary Studies: Over the last decade, the research team has focused on improving decision making for persons with serious illness, with a particular focus on cancer and pediatrics, by creating and studying innovative decision aids. The work cited below demonstrates the research team's experience, commitment, and ability to effectively use a wide array of clinical research methods to design, administer, and complete projects focused on the care of patients with advanced illness and poor prognosis. The research team has also led some of the critical research work in pediatric cancer care. The studies below represent a systematic series of investigations that set the stage for this proposal.

2.2.1 Preliminary studies in cancer: The first video our team produced was a 5-minute decision aid depicting the GOC for adults with cancer.[27] In an RCT, patients with advanced cancer were randomized to either listen to a verbal description of the GOC (N=27) or view the video decision aid (N=27), and then asked the level of care they would want. The three levels of care included: life-prolonging care (hospitalization, intensive care unit); limited/selective care (hospitalization but no ICU); or comfort care (symptom relief only). We also assessed uncertainty regarding decision making using the Decisional Conflict Scale with scores ranging from 3 (high uncertainty) to 15 (no uncertainty). End points were the selected GOC, uncertainty in decision making, and comfort viewing the video. Patients in the video arm (vs. control) were more likely to opt for comfort, were more informed, and more certain of their decision. Among patients receiving the verbal narrative, 26% desired life-prolonging care, 52% chose limited/selective care, and 22% preferred comfort care (see Figure 2). In the video group, none desired life-prolonging care, 4% chose limited/selective care, 92% preferred comfort care, and 4% were uncertain (P < 0.001). Participants in the video group had less uncertainty (mean uncertainty score, 13.7; [95% CI, 12.8 to 14.6]; P = 0.002) compared to participants randomized to the verbal group (mean uncertainty score, 11.5; [95% CI, 10.5 to 12.6]). Of the patients randomized to the video group, 82% felt “very comfortable” watching the video, and 82% would “definitely recommend” the video to other patients.

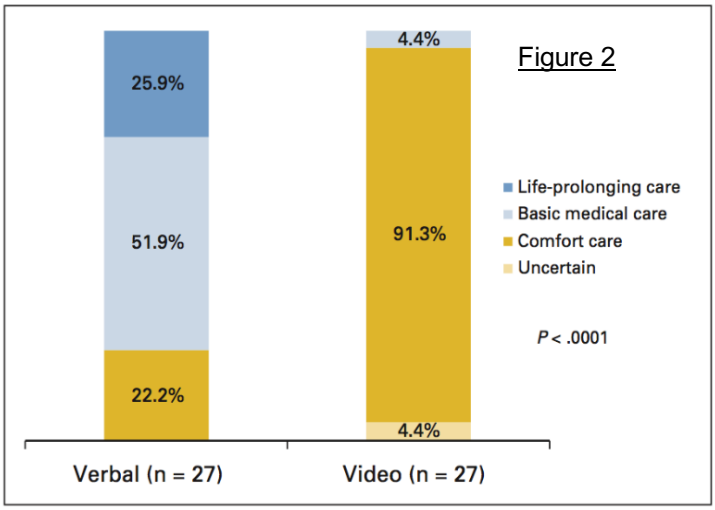
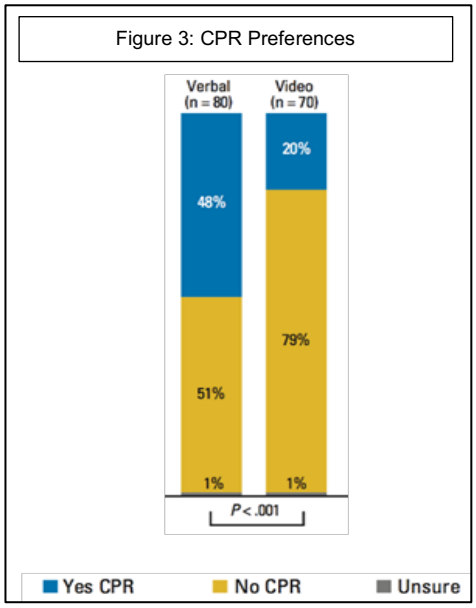


Figure 2

Based on this work, the research team completed a larger NCI-funded trial in adult patients that was published in the *Journal of Clinical Oncology* and presented as an oral abstract at the annual meeting of the American Society for Clinical Oncology.[22] In this multi-center randomized trial of a video decision aid exploring CPR, 150 participants were randomly assigned to either a verbal description of CPR (N=80) vs. the video decision aid (N=70) explaining the risks and benefits of CPR (see Figure 3). Health literacy was also measured using the Rapid Estimate of Adult Literacy in Medicine (REALM) tool. In the verbal arm, 48% of participants wanted CPR vs. 20% in the video arm (P < 0.001). Furthermore, patients watching the video were more knowledgeable (score range 0-4, mean video score, 3.3 ± 1.0; mean verbal score, 2.6 ± 1.3; P < 0.001). Of the patients who viewed the video, 77% would "definitely recommend" the video, and 20% would "probably recommend" the video. In a multivariate logistic regression model, random assignment to the video (adjusted OR [aOR], 4.7; 95% CI, 2.1 to 10.7) and higher health literacy level (7th-8th grade vs. < 6th grade: aOR, 3.6; 95%CI, 1.1 to 12.0; > 9th grade vs. < 6th grade: aOR, 3.8;95%CI, 1.3 to 10.8) remained independently associated with a preference for more comfort-oriented care and to forgo high-intensity interventions. These findings suggest that patients with low health literacy may particularly benefit from the use of tailored decision aids to explain GOC.

Figure 3: CPR Preferences



Using the above preliminary work in adult patients with cancer, the research team based out of Massachusetts General Hospital and Dana-Farber Cancer Institute is leading a large pragmatic trial of the video decision aids in more than 20,000 patients with cancer at 39 oncology clinics (UG3/UH3 AG060626-01).[92]

2.2.2 Using video decision aids in patients with cancer quadruples hospice utilization: We recently completed a randomized trial assessing the impact of a video decision aid on hospice utilization in patients with advanced cancer.[85] Patients receiving the video were more likely to utilize hospice (85.2% vs. 63.6%; P = 0.01) and had longer hospice length-of-stay (median 12 vs. 3 days; P < 0.001) compared to those receiving usual care. Patients in the video group also reported greater knowledge about hospice and more favorable perceptions of hospice care. Caregivers of patients assigned to the video were also more likely to prefer hospice for their loved ones (94.4% vs. 65.4%, P = 0.03), reported greater knowledge about hospice, and were more likely to have favorable perceptions of hospice care. Our intervention promotes education in the different GOC and leads to increased hospice utilization for those with advanced cancer.

Using video decision aids in adolescents and young adults with cancer: The research team recently completed an NCI-funded (1R21CA234708) pilot randomized trial assessing the impact of a video decision aid on GOC knowledge in adolescents and young adults with cancer. Fifty patients with cancer aged 18-39 were randomized 1:1 to the video or usual care. Patient-centered and clinically meaningful outcomes including GOC knowledge, readiness to discuss GOC, and decisional conflict for future care were obtained pre- and post- intervention and compared between groups. Patients in the video arm showed greater change in mean knowledge (0.6 vs. 0.3), readiness scores (1.2 vs. 0.6), and improved decisional conflict (0.7 vs. 0.1) compared to controls. The video was highly rated by patients: 95% found the video helpful, 95% were comfortable viewing the video, and 91% indicated they would recommend the video to other

patients facing similar decisions.[122] A video-based GOC tool was well-liked by patients, resulted in increased GOC knowledge, less decisional conflict, and more GOC readiness.

Significant work in young children with cancer and documenting the need for improvement in pediatric GOC communication: Our research team has been at the forefront of conducting clinical trials involving young children with cancer and their parents. We successfully completed a multi-centered RCT evaluating whether providing e-PROMs feedback (symptom and HRQoL [Health Related Quality of Life] summary scores via a paper report) to families and clinicians of children with cancer, improved child's HRQoL and symptom burden. In the intervention arm, *all* scores changed in the expected directions but changes were small, not reaching statistical significance. In post-hoc subgroup analyses looking at older children and those who survived 20 weeks, larger improvements in almost all scores were observed in the intervention group, especially in emotional PedsQL scores.[124] This study was among the first palliative care trials in children with cancer successfully demontrating feasibility.[125] Notably, enrolled parents reported highly valuing palliative care studies and that their primary reason for enrollment was helping other cancer patients and their families. We have also just completed accrual for a follow-up trial pairing e-PROM symptom and HRQoL feedback with intervention by a specialty palliative care service in four large pediatric cancer centers. Our research group has also shown that pediatric clinicians identify numerous barriers to holding GOC discussions with families of seriously ill children and believe parents are not ready for such discussions.[126] We also demonstrated the unintended consequences of limited GOC discussions in seriously ill children and their families.[5] Specifically, without GOC discussions parents are less likely to be prepared for their child's last days and are less able to plan their child's location of death and quality of life. In contrast, when discussions involve specific assessment of family goals, the child is less likely to experience suffering at the end of life (adjusted odds ratio 0.23; 95% CI 0.02-0.87). As such, there is a critical need for interventions that educate and prepare parents for GOC discussions.

2.2.3 Using NLP for obtaining GOC outcomes in pediatric patients with cancer: To rigorously assess outcomes in a trial of this scale, we will use rule-based NLP to query large volumes of EHR data. In a paper presently under review, we used NLP to identify GOC conversations documented in physician notes during hospital admissions. The NLP algorithm was developed and validated on a dataset consisting of 641 notes (containing 895,328 tokens) from 402 patients. For detecting GOC documentation at the note level, the algorithm had a sensitivity of 93.5% (95% CI, 90.0%-98.0%), and a specificity of 91.0% (95% CI, 86.4%-95.3%). Based on this and other work, we further refined the NLP-assisted and human-confirmed approach. In our ongoing U-grant pragmatic trial (UG3/UH3 AG060626-01), we validated our NLP approach compared to human coders. Specifically, we compared the ability of two coders who manually reviewed 981 EHR notes for 30 patients compared to the results of our NLP-assisted and human-confirmed approach.[127] There were no reviewer-identified outcomes that were not identified by NLP (i.e., 100% sensitivity). Every false positive was excluded by human review (resulting in a specificity of 100%) or included as a true outcome, representing events missed by manual chart review. In this study, manual abstraction of GOC outcomes took the chart reviewer approximately 30-120 minutes per patient. In contrast, NLP analysis of each patient's compiled clinical notes took 1-5 minutes. Our research team is also the first to study the use of NLP in pediatric oncology. In a manuscript presently under review, we validated the rule-based NLP in the pediatric cancer setting. We conducted a single center cohort study of children aged 0-25 years who died of cancer between January 1, 2014, and December 31, 2022, while receiving care at Yale New Haven Children's Hospital/Smilow Cancer Hospital, a National Cancer Institute-designated cancer center. Our study cohort consisted of 101 childhood cancer decedents with 29,934 notes from the last six months of life. First, we randomly selected a 10% sample of decedents and conducted a manual chart review of all clinical notes in the last six months of life in the EHR. These randomly

selected 10 decedents accumulated 5,076 notes in the last six months of life. We then ran the NLP software on the same set of notes. We validated the NLP software by comparing performance of the NLP to manual chart review in identifying documentation of GOC process measures in clinical notes. The manual chart review was considered the gold standard corpus in this comparison. We utilized a second random sample of notes from 10% of decedents to complete this process. We evaluated true positives, or NLP identification of a process measure that has also been identified in the gold standard corpus; false positives, or NLP identification of a process measure when absent in the gold standard corpus; false negatives, or when a process measure is present in the gold standard corpus but not identified by NLP; and true negatives, or when a process measure is uniformly absent in both the gold standard corpus and the NLP software. Performance statistics, including precision, recall, and F1 score, were then computed. Precision, or positive predictive value, is defined as true positives / true + false positives. Recall, or sensitivity, is defined as the true positives / true positives + false negatives. The F1 score is the harmonic mean of these values, calculated as 2* [(precision*recall)/(precision+recall)]. During the validation process, we continued to iteratively revise the keyword library to improve performance statistics. We aimed to achieve precision > 90% and an F1 score as close to 1 as possible, optimizing accuracy of the NLP pipeline. For our study cohort consisting of 101 childhood cancer decedents with 29,934 notes from the last six months of life, the validation data set assessed the performance of our refined keyword library ultimately achieving robust performance statistics (F1 score = 1.0 across all process measures). Compared to manual chart review, our NLP-assisted and human-confirmed approach is highly accurate and completed in a tiny fraction of the time.

2.2.4. Minority Sampling: Our research team has extensive experience with large pragmatic trials, implementation science, and recruiting African American, Hispanic, and rural patients and over the last decade has been a key member of the NIH Pragmatic Trials Collaboratory.[128,129] We are conducting three large pragmatic trials; all using video decision aids. The first is using video decision aids with navigators in the skilled nursing home setting using a cluster-randomized study design of 432 skilled nursing facilities. Of note, we recruited 1,692 African American patients for this study of older patients (UG3/UH3 AG049619-03).[130] The second is using video decision aids and navigators in a non-randomized pragmatic trial of over 15,000 older patients in ambulatory practices. Of note, we recruited 2,248 patients who identified as either African American or Hispanic (3UH3 AG060626-03S1).[86] Our third trial is implementing video decision aids and communication skills training in oncology practices in a large pragmatic trial of over 20,000 adult patients with cancer (UG3/UH3 AG060626-01; race/ethnicity data analyses pending).[92] We also have experience with recruiting patients in rural settings. Our research team was the first to study video decision aids in a rural population,[26] exhibiting similar patient-centered outcomes (improved GOC knowledge and improved communication with the health care team) as those found in our studies of urban populations. Further, our research team has extensive experience recruiting under-represented minorities in pediatric oncology studies through community partnerships and culturally adapted materials. We have conducted bereaved interviews to establish quality measures for children with cancer in both California and Alabama; in both sites we successfully sampled to have 50% represented minorities.[11] The research team has the depth and breadth of experience with large pragmatic trials, implementation science, and a highly successful track record of recruiting African American, Hispanic, and rural populations to successfully accomplish the aims of this study.

2.3 Summary

Our preliminary work shows that: 1. There is both a need and opportunity to improve the care of pediatric patients with cancer and their parents through better GOC discussions; 2.

Interventions to improve GOC discussions uniformly suggest that patients using the videos are more knowledgeable, more certain about their decisions, and more likely to have GOC conversations that lead to care delivery aligned with medical preferences; 3. Videos surmount barriers posed by language and limited health literacy; 4. Videos are a practical approach to improve GOC discussions that have been shown to be efficacious and can be implemented in health care systems; 5. Using navigators who have been trained in communication skills and using videos is a practical approach to improve GOC discussions that has been shown to be efficacious in several RCTs; 6. The research team has deep experience with NLP, pragmatic trials, and recruiting African American, Hispanic, and rural patients; and, 7. The investigators have experience conducting trials in young children with cancer.

3.General Study Design

The overall objective of this UG3/UH3 study entitled **Video Inspired Discussions for Ethical Outcomes in Pediatrics (VIDEO-PEDS)** is to build the infrastructure for and conduct a large randomized pragmatic trial of a GOC video decision aid in three diverse health care systems (Dana-Farber Cancer Institute, Children's Healthcare of Atlanta, and the University of Alabama). During the UG3 Phase (first two years), we will refine the GOC video decision aid, finalize clinics and workflows, train annotators on the NLP process, and pilot-test the intervention. During the UH3 Phase (subsequent four years), we will conduct a large, pragmatic, randomized, waitlist-controlled trial (RWCT) including 504 parents of children with cancer aged 0-12 years. This trial will include 76 African American, 76 Hispanic, and 76 rural children with cancer (45% of total enrollment) by design. Children will be randomized to Waitlist-Control or the GOC Video Intervention in which the video decision aid will be shared with their parents along with in-person and telehealth sessions conducted by navigators to elucidate GOC preferences. After the intervention period, the waitlist will open and all parents (i.e., Waitlist-Controls) will receive the intervention. Using NLP to detect outcomes (e.g., GOC documentation), we hypothesize that intervention children, as compared to controls, will have more GOC documentation (primary outcome).

4.Specific Aims and Objectives

Objectives for this proposal will be achieved via the following **Specific Aims**:

Phase UG3 Aims (Establish a trial infrastructure in three health care systems)

Aim 1: Guided by patient and clinician input, refine and finalize the GOC Video Intervention.
Aim 2: Finalize clinics and workflows to implement the intervention.
Aim 3: Train annotators on the NLP process using EHR notes.
Aim 4: Pilot-test the intervention and outcomes in 9 patients with cancer at each site to ensure feasibility.

Phase UH3 Aims (Conduct a large pragmatic randomized waitlist-controlled trial)

Aim 1: To compare GOC documentation in 504 children with cancer aged 0-12 years randomly assigned to our Video Intervention vs. Waitlist-Control. ***Hypothesis (H) 1a:*** *Children whose parents have been assigned to the intervention arm will be more likely to have GOC documentation compared to Waitlist-Controls during the intervention period.* ***H1b:*** *Intervention effects will be greater in African American, Hispanic, and rural children as compared with non-Hispanic, non-rural Whites.*

Aim 2: To characterize detailed patient- and parent-centered outcomes. ***H2****: Patients and parents in the intervention phase (vs. control) will have improved patient- and parent-centered outcomes.*

Aim 3: Using the RE-AIM QuEST mixed-methods framework, we will assess dimensions critical for consistent use, implementation, and adoption of the program in clinical settings using a mixed-methods framework.

1.1 Timelines

The study will take place over a 6 year period. The initial phases of development and piloting will happen in the first 2 years, while the RWCT will take place over years 3-6 (as shown in Table 1 below).

Table 1. Various Recruitment Aims of Phases UG3 and UH3 are outlined by the year of the grant

Phase	Year	Tasks
UG3	Year 1-2	**Focus Groups**, N=12 (Parents) **Pilot Study**, N= 13, 9 Parents and 4 Providers (Exit Interviews)
UH3	Year 3-5	**RWCT**, N=252 (EHR Data-Patient, Intervention-Parent, 3 cycles x 9 months each) **Consent Recording**, N=13 (fidelity of verbal consent) **Random Survey**, N=68 (survey at start and stop of each cycle, 1:1 both arms) **Stakeholder Interviews**, N=4 Parents, N=4 Clinicians, N=2 Clinical Leaders. (end of Year 6)
	Year 6	As above

*Accrual goals here are specific to DFCI, and site goals are variable for UH3.

Table 2. Development and Pilot PHASE (UG3): Timelines for various aims are outlined

Milestone ⚐	**Table 2: 24 Months of UG3 Phase**											
Infrastructure	0-2	4	6	8	10	12	14	16	18	20	22	24
Biweekly & Monthly Meetings												⚐
sIRB & Reliance Agremts.			⚐									
DSMB			⚐			⚐			⚐			⚐
Finalize UH3 Milestones												⚐
Pilot-Testing												
Focus Groups						⚐						
Refilm & Finalize Video						⚐						
Train Navigator						⚐						
Finalize Clinics									⚐			
Define Workflows						⚐						
Train Annotators									⚐			
Pilot Intervention											⚐	

Finalize GOC Intervention												⚑
Finalize Workflows												⚑

4.2 Study design of parent focus groups: 3 focus groups of 3-5 parents will be held. (Screening and Consenting procedures are detailed in section 5.2 and 5.3 below). One of these will be in Spanish, and populations will represent that intended for the eventual RCT (so we will target to include15% African American, 15% Hispanic, and 15% rural, based on feasibility of sampling. Of note, rural participants may be recruited for the English or Spanish focus group.) Parents will join a 1-2-hour virtual focus group discussion via Zoom. The moderators, Drs. Snaman and Eche, will use a semi-structured interview guide in order to ask a series of questions designed to better understand the GOC informational needs of parents, but will also allow the flexibility to ask additional questions to probe on topics as they come up.[131] We will begin by asking about their GOC informational needs in general, purposively open-ended to uncover a wide range of responses, and then delve deeper into more specific questions about additional decision-making needs they might have, the perceived barriers to effective GOC discussions, how clinicians can understand those barriers, and interest in learning about the different GOC medical decisions. We will explore the potential role of navigators, the comfort level of broadly discussing GOC with navigators, the topics preferred to be discussed with clinicians vs. non-clinicians (i.e., navigators), and the frequency with which interacting with navigators would be of value. The group will also view a GOC video decision aid that discusses GOC broadly focusing on values (e.g., quality of life and quantity of life), including spiritual and religious values, and specific interventions (e.g., CPR, intubation). One Spanish-language focus group will be held remotely at each site by Drs. Dussel and Volandes as they have done in prior work.[87,132,133] The Spanish focus groups will follow a similar format as the English focus groups.

After viewing the video, parents will be asked to rate on a Likert scale how much this video met their decision-making needs, was understandable, and if they would recommend it to others in their position; we will then ask them open-ended questions to further discuss their ratings. Please see the Parent Focus Group Semi-Structured Guide.

Focus groups will be audio recorded on Zoom Business accounts and stored on secure password protected encrypted devices as further detailed below in the data management section. All transcription of audio will be done in MAXQDA, for qualitative analysis of major themes.

4.3 Refilming of video decision aid: As we have done in prior work,[135,136] Drs. Volandes, Davis, Paasche-Orlow, Eche, and Dussel will refilm the video decision aid in English and Spanish based on the analyses as described above. Consistent with our prior refinement of videos, we expect changes in GOC themes covered, images used, and new content added. Our research team has considerable experience in refilming videos and incorporating focus group feedback. After a preliminary refilmed video is created, we will have an additional abbreviated (1 hour) focus group for an iterative process of comments and editing. (Only Part B of the same Parent Focus Group Semi-Structured Guide will be used and is approximated to take less than an hour.) A subset of the 36 parents (12 per site) will be invited in order to include 12 (3-5 parents per site). A link to the improved version of the video will be emailed to these participants if they are unable to see the video over the Zoom call. HIPAA compliant Video cards can also be pre-arranged if there are barriers to internet or devices identified. It is assumed only a subset of these parents will reply to the initial follow-up focus group invitation. A reminder will be sent if there is no response after a week.

4.4 Parent Advisory Board: Parents of children aged 0-12 with cancer will play an essential role in all aspects of this trial. The perspective of parents, who have had or have a child with cancer, will be and has been a key part of the development of this proposal and a major impetus to conduct this study. Three parents from each health care system, who have had or have a child with cancer in the last three years, will be identified by each of our three site-PIs (Drs. Snaman, Johnston, and Brock). Diversity in race, ethnicity, and gender will be prioritized. Dr. Eche, who has expertise in community engagement, will ensure best practices for community engagement to ensure all voices are heard. Furthermore, the Pediatric Patient and Family Advisory Councils (PPFAC) at Dana-Farber Cancer Institute and Massachusetts General Hospital (Mass General for Children) will facilitate the active participation of the Parent Advisory Board during the UG3 and UH3 Phases. The Parent Advisory Board will play an important role in ensuring that all aspects of the trial remain patient-centered and clinically significant by meeting annually.

4.5 Pilot Intervention Components

We will pilot-test the GOC Video Intervention at each of our three clinics at each site (i.e., 9 parents total at each site with all parents receiving the intervention). GOC conversations with the Navigator (explained further in 4.5.1) will be audio recorded for quality assurance and training (with parental verbal consent). They will experience an abbreviated 3 month study duration in which the Navigator will communicate with them (versus the 9 month RWCT). These 9 parents will be asked to complete exit interviews. Their primary providers will also be invited to do so (with a goal of hearing from 4/9). Audio recording may be done via a pre-tested handheld device (to be stored in a locked file cabinet in a locked office on site) if completed by phone or in-person. Others will be recorded by Zoom audio if the participant prefers to meet via video-conferencing.

We will also pilot our brief survey, which should take parents approximately 5 minutes to complete.

- Parent Feeling Heard and Understood: We will ask five validated items regarding "feeling heard and understood" (e.g., I felt heard and understood by the oncology team. I felt my child was heard and understood. I felt the team put my child's best interests first. I felt the team saw my child as a person. I felt the team understood what was important to my child).[161] Each statement is rated on a five-point Likert scale.
- Parent Satisfaction with Healthcare: We will use two items from the Survey about Caring for Children with Cancer (SCCC) to assess satisfaction with healthcare.[35] The first assesses the care team's sensitivity to the child's needs (response options: a great deal, a lot, somewhat, a little, not at all). The second assesses quality of care delivered by the care team (response options: excellent, very good, good, fair, poor).

Our **GOC Video Intervention** is a combination of a **video decision aid** and **navigator**.

4.5.1 The Navigator

A member of the research team at each site will serve as a Navigator. They will go through standardized training in VitalTalk, delivery of procedures through comprehensive Standard Operating Procedures (being developed with the PI and PM) and receive ≥ 8 hours of witnessed training including role-playing to demonstrate mastery of materials. Using lay coaches as navigators is a major strength towards scalability if the trial results show promise.

For parents piloting or randomized to the intervention, they will meet at an in-person clinic visit or via Zoom (on an institutional / business account that is HIPAA compliant). The navigator will then have structured, iterative, and longitudinal GOC conversations to support parents' understanding and encourage deliberation regarding GOC decision making in a manner that is sensitive to and respectful of cultural diversity regarding GOC decision making. To this end, the navigator will begin by asking if the parent has any questions about GOC in general. The navigator

will then use a structured framework, which we have used in our prior trials (1R01AG072911 and 3UH3AG060626) and also studied by others,[170-173] to facilitate the GOC conversation, but discussion will not be limited to pre-determined topics. The navigator will determine within the first few minutes of the encounter the timing of showing the video decision aid to explore general GOC values and to explore level of care and specific interventions. As in our other trials, videos are shown early during the encounter to spark a discussion and reflection. Navigators will show the video on a tablet or iPad if in person.

The navigator will then engage the parent in the following topics (As outlined in the submitted Navigator GOC Conversation Guide) since they are critical to providing medical care that is aligned with individual preferences: 1) What do you feel is most important for your child? What makes your child happy or gives them joy?; 2) What do you worry about regarding your child getting sicker and needing more medical care? What symptoms concern you the most?; 3) Are there any medical interventions that you feel strongly about, that you may or may not want for your child? Are there any that might be too much?; and 4) In times of difficulty, where do you find your strength? Do you have any religious, spiritual, or cultural beliefs that might guide choices about your child's medical care? In addition, the navigator will explore the video viewing experience. In general, the GOC conversation will explore initial feelings about GOC and then transition towards the video viewing experience (e.g., How did watching the video make you feel? What thoughts did the video provoke?). This will help gauge how interested the parent is in discussing their preferences further or if they would rather defer decisions until they consult with others (e.g., family, religious advisor, primary clinical team). If the parent is comfortable with further discussion, the conversation will be guided by the following topics, which may be covered in future interactions: 1) whether the parent perceived that having a GOC conversation is important at this point in their child's medical care; 2) reviewing the value-based questions presented in the video to help the parent focus their decision making; 3) further explaining the GOC; and, 4) if appropriate, eliciting the parent's GOC preferences. Exploring these topics with the parent may lead to a conversation about the importance of completing an advance directive/POLST with the primary clinical team. The navigator will encourage the parent to make their wishes known to their primary clinical team. Parents will have access to the video decision aid after the visit as described below.

The role of the navigator is to engage parents in a general GOC discussion that focuses on values. The navigator (who is not a clinician) is not positioned to accept or reject a parent's choice but instead positioned to start a discussion by introducing the general GOC themes. The navigator will then communicate with the primary clinical team the summary content of the discussion surrounding GOC. It is up to the primary clinical team to further discuss the GOC and whether they align with the actual needs of the patient.

The navigator will check-in with the parent as needed via email, telehealth, or in-person after the in-person visit, but at least once, at minimum, over the course of the intervention (nine months, or three in the case of the Pilot phase). The cadence of check-ins will not be pre-determined (reflecting actual clinical care and maximally pragmatic) and may change over time as GOC needs of the child change over time (e.g., change in functional status or acute illness). All three of our health care systems use EHRs that include two key native EHR functions: (1) An updated panel of children with scheduled calls and reminders, and (2) Automatic notifications of health status change of any child on their panel (e.g., hospitalization, urgent care visit, critical data). Thus, navigators will leverage the native functions of each health care system's EHR to follow their panel of children. Number and length of all in-person or telehealth (audio or visual) interactions will be documented in REDCap, allowing for additional analyses based on "dose" of the intervention (e.g., how many contacts the navigator had with the parent). Navigators will have flexibility to address the needs of any individual parent (e.g., frequency of calls, topics addressed, etc.) but will follow the above GOC iterative framework over the course of the intervention that

was used in our prior work. Parents will have the contact information of the navigator should they wish to schedule additional telehealth or in-person visits.

Telehealth is widely used at our three health systems in response to the pandemic and includes telephonic and audio-visual telecommunication. As an accepted part of patient-clinician interactions, telehealth has remained a permanent fixture for our three health systems. All navigators will undergo training in telehealth best practices by Dr. Michael Paasche-Orlow, a national expert on telehealth and video decision aids. Each of our health care systems report over 99% of patients have telehealth (audio or audio-video) capabilities. In the rare case that a parent does not have access to audio (i.e., telephone), the navigator will provide an inexpensive disposable phone with pre-paid card for follow-up visits.

At the initial visit, navigators will assess how a video will be shared with the parent for home use. The video can be shared through telehealth, and when telephonic, a link to the video can be texted via smartphone or emailed to patients or provided through the EHR portal. This means of disseminating videos was widely used in our prior studies with great success. For parents who do not have access to a smartphone, internet, or other means to watch a video, the video will be given to parents using a disposable videocard player that will be provided by the navigator at the in-person visit. Videocards are inexpensive, similar in size to a standard tablet screen, allow for the videos to be uploaded, allow tracking of use, and have a 10-hour battery life (that is rechargeable). Thus, all patients will have access to the video decision aid; digital access and literacy will not be a barrier to the GOC Video Intervention.

The navigator will engage the parent(s) in GOC discussions and provide educational support using the video. Navigators will be staff members of their respective health systems and will help coordinate GOC decision making and medical care with the child's primary medical team. They will prompt the primary clinical team in engaging with the parent regarding GOC that reflect the parent's wishes. Independent of the work and function of the navigator, all clinicians will be able to place requests for palliative care consultation. A key part of this pragmatic trial is the integrated role of the navigator.

For the Pilot portion of the study, the follow-up duration will be 3 months versus the full 9 months anticipated for the larger trial.

1.

4.5.2 Video decision aid

The video decision aid that will be discussed in the focus groups is available in both English and Spanish. (Note that Spanish materials for this study will be provided to the IRB in a subsequent amendment.) The decision aid followed a systematic approach, using an iterative process of reviews by oncologists, palliative care physicians, pediatric specialists, intensivists, and decision-making experts, regarding the design, content, and structure of the video. The decision aid was designed using the internationally recognized decision aid criteria to which our team was a contributor (International Patient Decision Aid Standards[134] [IPDAS], http://ipdas.ohri.ca/). Our research team members have been pioneers in the creation of video decision aids, and we have published widely on the use of videos to inform patients and families in an unbiased fashion.[135,136] The decision aid was developed with content that is intended to be objective and balanced. It is scripted at a fourth-grade level of health literacy in both English and Spanish and has closed captioning. The Spanish script was also back-translated into English to ensure cultural appropriateness and accuracy. A Certificate of Accuracy will be provided in our IRB submission.

The decision aid first discusses GOC broadly focusing on values (quality of life and quantity of life), including spiritual and religious values. The video, which is narrated by a physician, presents a general understanding of the GOC process, the questions that parents of children with cancer should reflect upon to elicit values and beliefs, and specific questions to ponder. The video begins by establishing the importance of the parent's personal values and perspective by asking the viewer four questions: 1) What do you feel is most important for your child? What makes your

child happy or gives them joy?; 2) What do you fear about your child getting sicker and needing more medical care? What symptoms concern you the most?; 3) Are there any medical interventions that you feel strongly about, that you may or may not want for your child? Are there any that might be too much?; and 4) Do you have any religious, spiritual, or cultural beliefs that might guide choices about your child's medical care? The images accompanying the questions reflect the questions asked and the potential scenarios.

The second part of the video explores the three GOC with a focus on interventions associated with each of the three goals. The physician-narrator introduces the three general GOC (life-prolonging care, limited/selective medical care, and comfort-focused care). The subsequent narration and visual images characterize these three goals. The visual images illustrating life-prolonging care include interventions that are available in a modern-day hospital such as CPR, intubation, mechanical ventilation, and treatment in the ICU. The second option, limited/selective medical care, is described as providing medical treatments that may be life-prolonging but do not subject the child to intensive care. This may include hospitalization, intravenous medications, and antibiotics, but not CPR or ICU care. Visual images include a seriously ill child getting medicine via a peripheral venous catheter, scenes from a typical medical ward, and a child wearing a nasal cannula and receiving breathing treatments. The third option, comfort-focused care, is described as aiming to maximize comfort and to relieve pain. Only measures that provide comfort are performed, and it includes a review of hospice care. Comfort care is compatible with oxygen and analgesics, but not with hospitalization unless necessary to provide comfort or based on an identified family preference. Visual images include a child on hospice care at home receiving pain medications, and a child with a respiratory face mask receiving oxygen at home. All three sequences of video images accompanying the narration attempt to help the viewer imagine the experience and likely outcomes of the three general GOC. The video was filmed and edited by the research team without the use of prompts or stage directions to convey a candid realism in the style known as cinema verite.[136]

A major strength of the VIDEO-PEDS study is that the video decision aid is available in both English and Spanish. The process of culturally tailoring GOC video decision aids to the Spanish language and culture is a major innovation of this study. Over the last decade, our team has developed a transcreation process to *translate* and then *create* tailored video decision aids for Spanish-speakers. The transcreation process is based on user-centered design[137] in which the team uses a mixture of investigative methods and tools (e.g., surveys, interviews, focus groups) and generative ones (e.g., brainstorming) to develop an understanding of user needs.[136,137] Our interdisciplinary team includes cultural anthropologists, ethnographers, film-makers, medical interpreters and translators, among others. The first phase of transcreation includes a scoping review of published materials on medical decision making and GOC, followed by focus-groups and transcriptions of interviews with patients, caregivers, clinicians, cultural experts (e.g., religious leaders, etc.) regarding GOC and the explanatory framework[138] that Spanish-Speakers use for illness. We then take the original English script and based on a cross-cultural adaptation process developed by Beaton et al.,[139,140] we perform the following: (i) Independent translation of the original by two bilingual native speakers; (ii) Synthesis of the two translations into a first consensus language version; (iii) Back-translation into English; (iv) Expert committee's assessment based on investigative methods, analyses and results; and finally, (v) Qualitative assessment by focus groups. Once a finalized script is crafted, filming begins including narrators, patients, families, and clinicians living in the U.S. that are native to the culture and language. The choice of scenes and camera angles have been described in detail by our research team and are the national standard that others have used.[135,136] The preliminary video is then reviewed and edited by parents, the Parent Advisory Board, and then by clinicians.

Our goal will be to ensure that the intervention is appropriate as well as useful to parents and the clinical staff before we conduct the larger pragmatic trial. During this pilot, we will also make sure that we have optimized our ability to identify and curate a list of eligible patients and to obtain oncologists' approval for parent participation with minimal staff burden. We will refine all workflows relating to the initial visit with navigators, and also assess whether showing videos at the in-person first visit was successful or if giving links to the videos is more appropriate. We will also ensure that videocards are available and are successful in surmounting issues relating to digital literacy and internet access.

4.6 Randomized Waitlist-Controlled Trial (PHASE UH4)

The overall goal of the VIDEO-PEDS proposal is to conduct a large, pragmatic, randomized, waitlist-controlled trial (RWCT) of 504 parents of children aged 0-12 with cancer. Participants will be randomized 1:1 to Waitlist-Control or the GOC Video Intervention in which a video decision aid will be shared with parents along with in-person and telehealth sessions conducted by trained navigators to help elucidate GOC preferences.

We will use the RWCT study design in which eligible parents are randomized to either Waitlist-Control or to the GOC Video Intervention for nine months (See Figure below for schema). After nine months of the intervention period, the intervention ceases for Intervention parents, and the Waitlist-Control parents come off the "waitlist" and receive the intervention for nine months.

Random assignment: We will conduct three cycles of the nine-month RWCT. Thus, over the course of 27 months, three cycles of unique patients will be randomized (9 months per cycle x 3 cycles = 27 months). The recruitment period is 36 months to account for the last nine months of intervention for Waitlist-Controls in the last cycle. We will examine data on a total of 504 children with cancer and their parents over the course of the four years of the UH3 Phase. At the start of each our three cycles, we will ask each health system to curate and finalize a list of all eligible patients. Each cycle, one-third of the total 504 children (i.e., N=168) will be randomized in 1:1 assignment, stratified by health system and demographic characteristic (African American, Hispanic, and rural) to Waitlist-Control or GOC Video Intervention. For each cycle, there will be pre-specified subgroups of 25 African American (15%), 25 Hispanic (15%), and 25 rural children (15%). (Please note that 76 per subgroup over the course of three years ÷ three cycles ≈25 patients per subgroup per cycle, a very reasonable goal).

Race/ethnicity variables are based on the commonly used methods of self-identification within the EHR, and our three health care systems are within national guidelines for reliable race and ethnicity data.[162] Race/ethnicity will be of the child; thus, parents may be a different race. Rural will be defined using the U.S. Census method.[163] Within the rural subgroup, we will include by design 15% (N=11) African American rural children and 15% (N=11) Hispanic rural children. In 2021, 24% (105 children) of rural children were African American and 18% (75 children) of rural children were Hispanic, making the proposed recruitment numbers for rural African American and rural Hispanic children high feasible. At the start of each of our three cycles, a new list of eligible children with cancer will be curated since this will change over time (i.e., every nine months).

Waitlist-Controls: Participants randomized to Waitlist-Control will use existing procedures in place at their health care setting (i.e., usual care). Presently, there are no system-wide GOC initiatives at our three health care systems. We recognize that over the course of the trial, our three health systems might use other programs or initiatives intended to improve GOC discussions. However, this is what "usual" care reflects in a pragmatic trial. Navigators (in the capacity of that role) will not interact with any Waitlist-Controls during the intervention phase. The navigators will not actively monitor the waitlist-control patients during the control period. Thus, lack of GOC

discussions and documentation may affect care in the waitlist-controls during the control period; however, this is the standard of care.

4.6.1 RWCT Schema

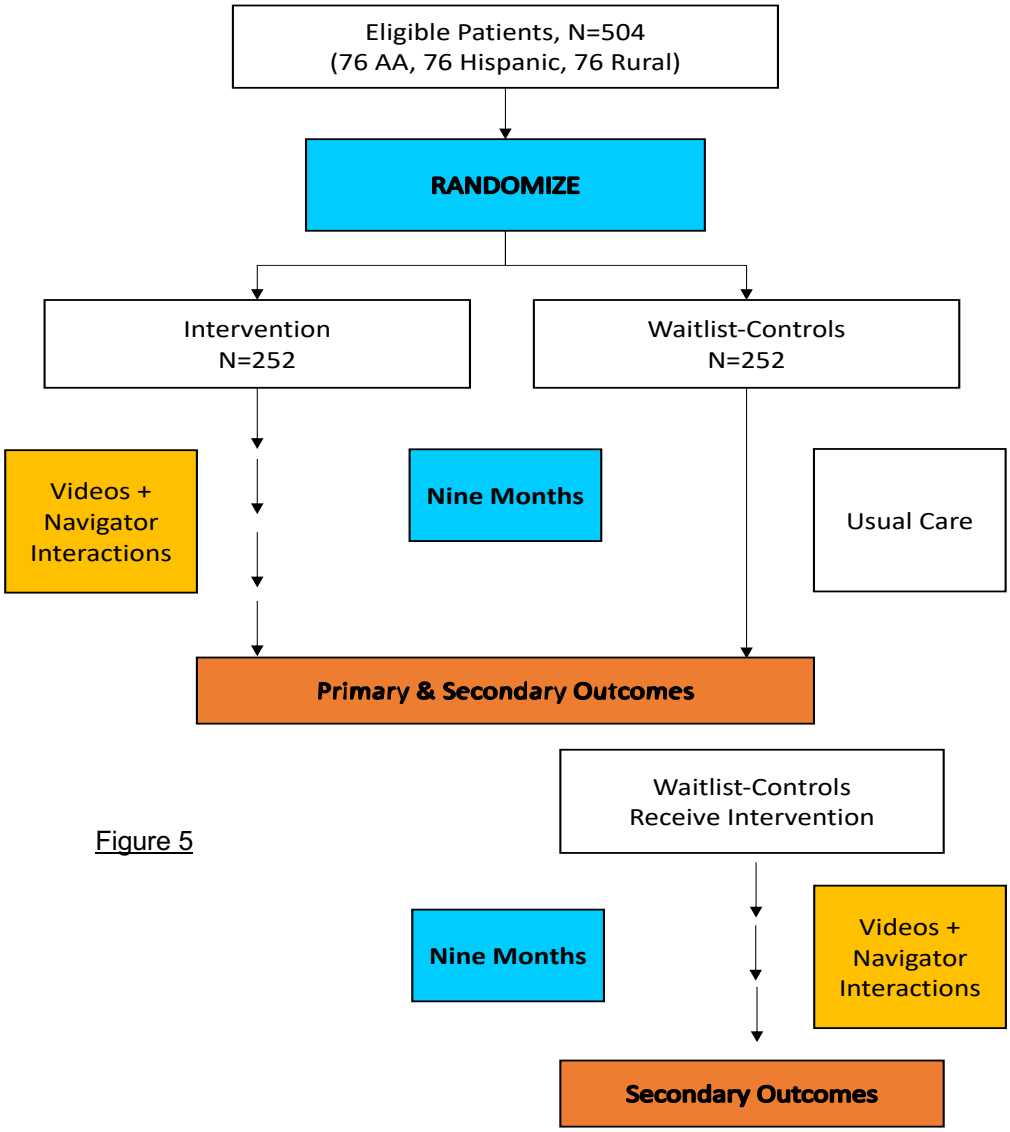


Figure 5

5. Subject Selection

There are three types of subjects who will participate in this study:

(1) Patients (via EHR only; N=504) - Patients aged 0-12 years diagnosed with cancer in one of the ambulatory cancer clinics involved in this study at Dana-Farber Cancer Institute/Boston Children's Hospital (N=252), Children's Hospital of Atlanta/Aflac Cancer Center (N=126), and the University of Alabama in Birmingham (N=126). From within the pool of these 504 participants, randomly half of the participants in each stratum (See Table 1) will start the intervention at the beginning of one of the three nine-month cycles, and the other half will be on the waitlist. After nine months, the waitlist is opened and all patients (i.e., their parents) will receive the intervention until the end of the subsequent nine months of participation. Data from electronic medical records will be used to ascertain: (a) GOC documentation; (b) medical orders for resuscitation preferences; (c) health care utilization; and (d) palliative care and hospice use. These participants do not interact with navigators nor do they watch any video decision aids. We will only interact with the children's parents.

(2) Parents of children with cancer – We will interact with parents of children with cancer in different ways throughout the UG3 and UH3 Phases. See section 2 Tables 1 and 2 below.

2a. Focus Groups (N=36) (UG3): Parents of children with cancer will participate in focus groups in which they will describe their informational needs for their children with cancer regarding goals of care. They will also view GOC videos that are designed to empower parents. We will recruit 12 parents from each of our three recruiting sites.

2b. Pilot Study (N=27) (UG3): Parents of children with cancer will participate in a pilot during the end of the second year of the UG3 Phase. Nine parents from each site will be recruited to undergo the GOC Video Intervention including viewing the video and speaking with a navigator. They will be invited to participate in exit interviews.

2c. Randomized-Waitlist Controlled Trial (N=504) (UH3): Parents of children with cancer will participate in the main trial of the UH3 Phase in which 504 parents will be randomly assigned to Intervention or Waitlist-Control over the course of three cycles lasting nine months each. At the end of each nine months, the waitlist will be lifted and Waitlist-Controls will also receive the Intervention. There will only be interactions with the parents; there is no interaction with the children. We will recruit 252 participants from our larger site (Dana-Farber Cancer Institute) and 126 participants from each of our two smaller sites (Children's Hospital of Atlanta/Aflac Cancer Center and the University of Alabama in Birmingham).

2d. Surveys (N=136) (UH3): A random sample of 136 parents of children with cancer will participate in a short survey during the UH3 Phase. The 136 parents will be evenly divided between the two arms of the study and the three study sites. They will receive the self-administered survey via email/mailing at the beginning of their nine-month period and again at the end of their nine-month period. We will recruit 68 participants from our larger site (Dana-Farber Cancer Institute) and 34 participants from each of our two smaller sites. These parents are already included in 2c.

2e. Stakeholder Interviews (N=12) (UH3): Parents of children with cancer will participate in stakeholder interviews at the end of the UH3 Phase. We will recruit 4 parents from each of our three sites. The stakeholder interviews will assess the acceptability of our intervention. We will ask parents to comment on perceived usefulness of the intervention, whether anything was learned, and how communication may have changed

with their clinician since the intervention. Prospective verbal informed consent will be obtained from parents. These parents are already included in 2c.

2f. Parents (via audio-recordings with navigators; N=25) (UH3): From within the pool of 504 parents, we will audio-record with verbal consent 5% of all interactions for intervention fidelity purposes (N=25). The recordings will be used by site PIs at each site for supervision, feedback, and learning purposes. In addition, a subset of recordings will be transcribed and analyzed. Some of these interactions will take place in languages other than English (i.e., Spanish). The consent process for these will be conducted with approved language appropriate methods and the resulting transcripts will be translated. Prospective verbal informed consent will be obtained from parents.

(3) Stakeholders (Qualitative Interviews; UG3 N=12, UH3 N=30) – We will invite the 9 primary providers we engage with for the UG3 pilot families at each site to participate in exit interviews. We anticipate completion of 4 interviews based prior response rates of similar trials, so 12 total interviews from the pilot intervention primary providers across sites. For the larger UH3 RWCT phase, we will target 30 stakeholder interviews (10 per site with 4 parents (already described in 2e), 4 clinicians, and 2 clinical leaders). Participants will be from ambulatory clinics involved in this study at our three health care systems to assess the acceptability of our intervention. We will ask parents to comment on perceived usefulness of the intervention, whether anything was learned, and how communication may have changed with their clinician since the intervention. We will ask clinicians and leaders about barriers and facilitators to the integration of the intervention into clinical workflow and to identify strategies for eventual dissemination. *These comprehensive Appendix Materials will be provided in an amendment after the development phase of the study.

Accrual Summary:

Site	Accrual		Total Accrual
DFCI	Parents: 12 focus group, 9 pilot, 252 RWCT (x2 for affiliated patient/ child)	Providers: 4 pilot, 6 RWCT stakeholders	556
UAB	Parents: 12 focus group, 9 pilot, 126 RWCT (x2 for affiliated patient/ child)	Providers: 4 pilot, 6 RWCT stakeholders	304
CHOA	Parents: 12 focus group, 9 pilot, 126 RWCT (x2 for affiliated patient/ child)	Providers: 4 pilot, 6 RWCT stakeholders	304
All sites			1164

Table 1. UH3 Child and Parent Strata Assignment to be Randomized to Intervention vs. Waitlist-Control (N=1008; 504 children and 504 parents)

				DFCI (n=504)	Atlanta (n=252)	Birmingham (n=252)
Non-Hispanic African American	Child	Rural	Male	0	2	2
			Female	0	2	2
		Non-rural	Male	19	3	3
			Female	19	13	11
	Parent	Rural	Male	0	2	2

			Female	0	2	2
		Non-rural	Male	9	3	3
			Female	29	11	13
Hispanic	Child	Rural	Male	0	2	2
			Female	0	2	2
		Non-rural	Male	19	8	7
			Female	19	8	7
	Parent	Rural	Male	0	2	2
			Female	0	2	2
		Non-rural	Male	9	3	3
			Female	29	11	13
Non-Hispanic White/Other	Child	Rural	Male	9	15	15
			Female	9	14	14
		Non-rural	Male	79	30	30
			Female	79	29	29
	Parent	Rural	Male	5	8	8
			Female	13	21	21
		Non-rural	Male	39	15	15
			Female	119	44	44

Table 2. Parent Strata for Focus Groups/Pilot (N=63) and Stakeholder Interviews with Clinicians and Leaders (N=18)

				DFCI (n=27)	Atlanta (n=27)	Birmingham (n=27)
Non-Hispanic African American	Child	Rural	Male	0	0	0
			Female	0	0	0
		Non-rural	Male	0	0	0
			Female	0	0	0
	Parent	Rural	Male	0	0	0
			Female	0	0	0
		Non-rural	Male	2	2	2
			Female	3	3	3
Hispanic	Child	Rural	Male	0	0	0
			Female	0	0	0
		Non-rural	Male	0	0	0
			Female	0	0	0
	Parent	Rural	Male	0	0	0
			Female	0	0	0
		Non-rural	Male	2	2	2
			Female	3	3	3
Non-Hispanic White/Other	Child	Rural	Male	0	0	0
			Female	0	0	0
		Non-rural	Male	0	0	0
			Female	o	0	0
	Parent	Rural	Male	2	2	2
			Female	3	2	3
		Non-rural	Male	6	6	6
			Female	6	6	6

5.1Inclusion/Exclusion Criteria

Eligibility for parent participation will be based on eligibility of their child; however, the parent will be the individual participating in focus groups and study activities during the UG3 and UH3 Phases.

Eligibility criteria for children with cancer and their parents will be the same for UG3 and UH3 Phases. Of note, for the pragmatic trial and for our primary outcome (GOC documentation), one or both parents (if present) will be involved in the GOC Video Intervention as this is the case in clinical care (and unlike our focus groups in which only one parent will participate). *For the subgroup of 136 parents who complete surveys, only one parent per child will participate.*

[4] **Eligibility criteria for <u>children</u> with cancer**: Children must meet all **inclusion criteria**: **1.** Age 0-12 years (in our three states, parents are considered surrogate decision makers for children; after 12 years of age, children begin to develop agency to partake in decision making); and **2.** Any child diagnosed with cancer. Our eligibility criteria are a considerable strength given that they are maximally pragmatic (all stages and types of cancer) and clinically relevant (i.e., GOC conversations are relevant for all patients with cancer). **Exclusion criteria include**: **1.** Any patient who is not receiving their medical care primarily from the cancer clinic (i.e., no second-opinion consultations); **2.** Patients under the care of family members or foster parents who do not have legal guardianship; and, **3.** Any child already referred to the palliative care team who had a full initial consult and was followed by the team, since a majority will already have documentation of GOC as a result of palliative care engagement; and **4.** Life expectancy less than 2 months since the study aims to changes in GOC documentation over time, but estimations of prognosis are poor beyond such a short period (eligibility will be confirmed by PI.)
[5]

Eligibility criteria for <u>parents</u>: We will recruit parents of pediatric patients with cancer for the focus groups (N=36; 12 parents from each of our three sites). Parents (or guardians) meeting all of the following **inclusion criteria** are eligible: **1.** The decision maker for their child; **2.** Biological parent, step-parent, or legal guardian (e.g., adoptive parent); **3.** Grandparent's medical consent form (e.g., grandparent authorized to make medical decisions); **4.** Has a child that meets the above child inclusion criteria; and, 5. Able to communicate in English or Spanish (the languages of our video decision aids). **Exclusion criteria include**: **1.** Visually impaired beyond 20/200 corrected and not able to view the video (note, hearing impaired is not an exclusion as the videos are closed captioned); **2.** Psychological state not appropriate for GOC discussions as determined by the primary oncologist. If there are two parents that are eligible for a single child, only one parent will be able to participate; and **3.** Participants who do not speak English or Spanish are excluded because these are the two languages of our video decision aids and the intervention is not yet validated in other languages

Eligibility Checklist for Child

Inclusion Criteria (All criteria must be met):

- Age 0-12 years
- Diagnosed with any type or stage of cancer

- Receiving cancer directed treatment

Note: Eligibility is maximally pragmatic and clinically relevant as GOC conversations are appropriate for all pediatric cancer patients.

Exclusion Criteria (Any one criterion excludes participation):

- Not receiving primary medical care from the cancer clinic (e.g., second-opinion consultations only)
- Under the care of family members or foster parents without legal guardianship
- Already referred to and fully consulted by the palliative care team
- Prognosis of less than 2 month life expectancy

Eligibility Checklist for Parents

Inclusion Criteria (All criteria must be met):

- Decision maker for the child.
- Biological parent, step-parent, or legal guardian (e.g., adoptive parent), grandparent with medical consent authority.
- Has a child meeting the child inclusion criteria listed above.
- Able to communicate in English or Spanish (the languages of the video decision aids).

Exclusion Criteria (Any one criterion excludes participation):

- Visually impaired beyond 20/200 corrected and unable to view the video (note: hearing impaired is not an exclusion as the videos are closed captioned).
- Psychological state not appropriate for GOC discussions, as determined by the primary oncologist per the opt-out.
- Participants who do not speak English or Spanish are excluded because these are the two languages of our video decision aids and the intervention is not yet validated in other languages

5.2 Screening Procedures

We seek verbal consent and request a waiver of written consent documentation.

For focus groups:
Potential participants will be identified by key informants: parents of children who meet the eligibility criteria detailed in section 5.1 will be identified by providers from the neuro-oncology, hematological malignancy and solid tumor teams. We will draw a purposeful sample to maximize variation and include critical cases in each of our three health care systems.

Potentially eligible patients will be entered into an excel "pool list." This screening strategy is equivalent to running a census of the base population and as such minimizes bias in identification of potential subjects and ensures that the pool of participants invited to participate is representative of the base population. RAs will screen medical records of children entered into the pool list to identify whether the child belongs to the base population. Children identified as potentially eligible will be assigned a study ID and entered into the VIDEO-PEDS REDCap screening and tracking database, adapted from our prior PQ-Response study to complete screening. (Of note, this REDCap will be built during the Development and Pilot UG3 phase of the study. Initial screening will progress in Excel during this preparation, for feasibility and so as not to delay the research.) The RA will complete an Eligibility Checklist of each criteria via a REDCap form that will then be emailed to the PI for confirmation. The response will generate a "Validation" email from the PI (serving the regulatory need for a screening Source Document). (Of note, this process can also be done manually via email until the REDCap is built.) We will email the disease program leader to request a blanket approval and authorization to contact providers' patients and ask that the providers specify any patients whose parent/guardian should not be approached. We provide clinicians with the opportunity to opt-out. If no opt out notice is received within 3 days (72 hours), families will be considered approachable for recruitment. If an out of office reply is received, we will contact a second clinician (such as a nurse or fellow on the patient's care team rather than waiting on their attending). In the case of participants referred by their primary provider, we will use an abbreviated process bypassing the optout process.

Children with cancer will be identified using their electronic medical record as described above. To conduct this screening procedure, parent participants will sign a separate HIPAA authorization. We will use ICD-10 codes and review the medical record.

5.3 Consent Procedures

We seek verbal consent and request a waiver of written documentation of consent.

We will enroll one parent per child, as designated by the family, and will suggest it be the parent who is formally or informally the primary caregiver. The consent process will include the following steps:

- During the first video or in-person meeting, the research assistant (RA) will introduce the study. The bilingual information sheets will assist the consent process. The RC will be trained in presenting the study using sensitive language without coercion or undue influence and allowing parents enough time to field questions. Potential participants will be encouraged to seek clarification regarding study procedures and efforts will be made to ascertain parent's understanding before inquiring about willingness to participate. The elements of consent will be addressed during this conversation.

- If a parent manifests interest in participating with their child, the RA will seek verbal permission for parental involvement, which will include medical record abstraction from the child and their own participation:

    - secure **verbal parental permission for** data collection (from medical record). We will not be able to seek assent or consent from participating children

  - separately ask for **verbal parent consent for their participation in the study** involving data collection (from surveys, interview, and medical record abstraction)

- The information sheet documents will contain all the required elements of an informed consent including a disclosure statement containing study details, information regarding the data that will be collected, when they will be collected, by whom, and how. The disclosure statement will also describe the child and parent's potential risks and benefits of participation.

- The study will recruit **Spanish speaking participants**. We will use language adapted study materials, as mentioned in section 4.2. and will integrate interpreters into the consent conversation of these parents. Interpreters will be called for in-person/phone services throughout the study through BCH interpreter services. Certified Spanish speaking members of the BCH study team will take point with the Spanish speaking families.

- **Risks for coercion or undue influence** will be minimized by: i) thorough training of RAs in using appropriate and sensitive language to explain the study goals and procedures and transmit that the decision to enroll is voluntary and will not affect regular care; ii) research staff that is unrelated to the primary clinical teams; and, iii) inclusion of email and virtual enrollment procedures, which in our experience have allowed for greater decision autonomy (unpublished).

- Parents who decline participation and those who do not answer the initial surveys, and are therefore not randomized, will be sent the **non-participation survey**.

- We request a **waiver of written documentation of consent for child and parent participation** based on the following considerations: (i) participating in the study, which involves answering surveys and one semi-structured interview, and in the case of participants assigned to the intervention constitutes "no more than minimal risk"; (ii) the rights and welfare of the subjects will not be adversely affected: study staff will present all the elements of informed consent during the consent process; (iii) increased study feasibility: most consent processes will occur virtually to accommodate better to parent's schedules. The need to sign and send a paper document will incur in unnecessary burden for parents. We have successfully used this consent method in our prior PediQUEST Response trial. The verbal consent (including permission to contact in the future) will be registered by the RA in REDCap.

- **Consent to contact at 6 months post-study**: As the post-study measurement point will only be done in a subgroup of participants (the first 12 enrolled), we propose to, rather than adding this evaluation to the study information sheet, re-consent this group of subjects during their exit interview, i.e. ask permission to contact them again at 6 months post-study to have them answer two surveys and a brief interview. Consent procedures for this portion of the study will mimic what was explained above including providing them with a specific information sheet that describes the procedures of this evaluation and the request of a waiver of written documentation of consent. Verbal consent will also be registered in our REDCap database.

For the RWCT, we request a waiver of written documentation of consent, except as otherwise delineated (if of the subset of the cohort also asked for audio recording).

(1) Parents for focus groups: Parents will be providing verbal consent but we request a waiver of documentation of consent given that this is conduct remotely and presents added burden to parents in a minimal risk study.

(2) Parents for pilot: Parents will undergo the video intervention with navigators during the second year of the UG3 year to pilot the intervention.

(3) Parents (Audio-recordings): For parents who will be subjects in this research for audio-recordings, individual verbal informed consent using an IRB approved script will be obtained. (This applies both to the 5% of Navigator conversations that will be recorded, as detailed further below, and the parent interviews and focus groups.)

(4) Stakeholders (Qualitative Interviews): Primary oncology providers will be informed through study staff about the purpose and procedures of the study using forums such as meetings, posters, or internal newsletters. With regards to the subset of providers who are invited to participate in the exit interviews, the elements of informed consent will be provided on the invitation email (see template submitted), including a statement about how information will be handled and stored and a section detailing our privacy and confidentiality safeguards.

We request a **waiver of documentation of consent for primary providers participating in the stakeholder interviews** based on the following considerations: (i) participating in the study, by either interacting with the Navigator as part of the intervention and/or participating in an interview to reflect on their experience with study patients and procedures, constitutes “no more than minimal risk”; (ii) the rights and welfare of the subjects will not be adversely affected: study staff will present to providers all the elements of informed consent during training and through exit interview’s invitation email; (iii) increased study feasibility: we would like to reduce the burden of participating for providers. Further, in the case of provider interviews, confidentiality is unlikely to be breached given that tapes and transcripts will be coded, securely stored, and de-identified (as detailed in sections below on Data Management and Confidentiality).

(5) Parents (randomized waitlist-controlled trial): As described above, we will secure verbal parental permission for child or adult child participation, involving data collection (from medical record) and being followed by the PPC team if assigned to the intervention. We will not be able to seek assent or consent from participating children because of their cognitive impairments, so rely on surrogate consent from the parent. Separately we will ask for verbal parent consent for their participation in the study involving data collection (from surveys, interview, and medical record abstraction) and meeting with the PPC team if assigned to the intervention. In accordance with the pragmatic trial of a minimal risk intervention that is being implemented as the standard of care for parents of children with cancer randomized to the intervention, and then applied to Waitlist-Controls after the intervention period is over. The data for our primary outcome and some of our secondary outcomes are derived from the EHR. Thus, for this aspect of our proposal, we will seek a waiver of individual informed consent and parent participants will sign a separate HIPAA authorization. The research involves no more than minimal risk to the subjects as described above. We do not believe the waiver will adversely affect the rights and welfare of the subjects. As a pragmatic trial of outpatients, this research could not practicably be

carried out without the waiver nor without access to and use of patients' PHI. Finally, we have developed a plan to protect identifiers from improper use and disclosure.

Parent participants will sign a separate HIPAA authorization.This will be needed to identify potential patient participants. It is our assessment that this study meets the regulatory requirements for the preparatory for research provisions of the HIPAA privacy rule (45 CFR 164.512) and will work with each institutional IRB and Privacy Officer to establish that this does meet the standards for the security of protected health information. In accordance with this provision, only researchers and staff who are a part of the "covered entity" will use the preparatory research provision to curate the list and then randomly assign children with cancer and their parents to their study trial arm. No identifiable PHI will leave any covered entity without consent and an approved procedure.

5.4 Retention Strategies

Strategies to enhance recruitment and retention will be implemented. Offering a variety of flexible options for participation helps with inclusion and recruitment success. RA support to facilitate study completion where requested or needed is key. Contact information will be provided to reach a member of the research team or the PI directly. We have highly motivated site-PIs, which is a key factor in ensuring access to this population of patients. We will also utilize the qualitative interviews with parents and clinicians to assess recruitment and retention facilitators and barriers and discuss how they can be addressed. We aim to reduce gate-keeping effects by educating oncologists about high family satisfaction with GOC discussions and the improvement in child-centered care delivery. Similarly, we anticipate more referrals by having broad eligibility criteria and having more educated clinicians about the study. Retention should be high because of the relatively short follow-up (or cross sectional timepoints in the case of focus groups) and having highly experienced navigators on the study. We similarly expect adherence to study procedures to be high.

6. Data Study Procedures

6.1 Data Variables and Data Collection Methods

Enrolled participants will be registered to Oncore, as Applicable DF/HCC policy (REGIST-101) must be followed.

Research material for this study includes screening/enrollment data collected for tracking purposes by the RA (including the inclusion and exclusion criteria, screening date and source, and some demographics as noted above), secondary screening and SOP documentation in REDCap (Eligibility Checklist, PI Validation, Provider Opt-Out, Approach, End of Study Checklist, etc.), survey responses in REDCap and response rates, and audio-recorded parent and clinician perspectives. RAs will receive 8 hours of training in study procedures to ensure high quality data collection. (Navigators will receive additional training as described above, including VitalTalk.)

6.1.1 NPL Outcome Measures

For the proposed trial, we will use NLP, a form of computer-assisted abstraction, to detect primary and secondary outcomes (e.g., GOC documentation). A rule-based software equipped with text annotation capabilities will be used to assess outcomes for the study. This software,

ClinicalRegex,[147] was developed by our research team. The software has been used to assess process-based quality measures in multiple studies across clinical settings.[110,112,148-160] ClincalRegex identifies all pre-specified keywords and phrases within a corpus of text (i.e., clinical notes). Human annotators then use ClinicalRegex's user interface and pre-specified annotation guidelines to interpret the documentation and to indicate whether ***the keywords and phrases identified by the software are in the appropriate context.***

Identification of Keywords and Phrases in Clinical Notes: A keyword library has been developed to identify keywords and phrases relating to the outcomes of interest (NLP domains) within the clinical notes and has already been validated in the pediatric cancer setting (See § 4.3 Data Analyses, Supplementary Table 1 and Table 2). Each NLP domain's keywords were defined *a priori* by clinical experts tasked with the question, *"how would you spontaneously write about this topic in the pediatric cancer clinic?"* Abstraction guidelines (i.e., guidelines used to determine whether a term from the keyword library that appears in a clinical note appears in the context pertinent to the study outcome(s)) with abstraction criteria and inclusive/exclusive examples, were then developed. For patients for whom the presence of the outcome is flagged as present using the NLP search, the annotator (i.e., RA, study staff) will review the flagged section of text to confirm that the documentation reflects GOC. Once these variables have been abstracted from the health care system's EHR, the data will be collected for each patient. The primary outcome of the trial will be ascertained through NLP-identified instances of GOC: GOC conversations, code status limitations, palliative care, hospice, and time-limited trials. Secondary outcomes for this trial will characterize care preferences, including documentation of preferences for resuscitation and intubation, enteral feeding, and dialysis. We will also use NLP to abstract additional secondary patient-centered outcomes such as use of palliative care and hospice. We will also look at the number and timing of high-intensity, burdensome treatment utilization from the EHR (CPR, intubation, etc.), as well as emergency department visits and location of death, when applicable.

Domain	Outcome	Definition	Annotation Criteria
Goals-of-Care Discussion	Primary	Conversations with patients or support persons regarding the patient's goals, values, or priorities for treatment and outcomes. As well as the evidence that elements of advance care planning were discussed, reviewed, or completed.	0 = No discussion 1 = Discussion
Code Status Limitations	Primary	Limitations to cardiopulmonary resuscitation and intubation.	0 = No limitation 1 = Limitation
Palliative Care	Primary	Mention of a visit with a specialty palliative care clinician, mention of specialist palliative care discussion, or patient preferences regarding seeing a palliative care clinician.	0 = No discussion 1 = Discussion
Hospice	Primary	Statements mentioning a discussion of hospice, prior enrollment in hospice, patient preferences regarding hospice, or assessments of hospice eligibility.	0 = No discussion 1 = Discussion
Time-Limited Trial	Primary	Conversations with patients or family members about the use of a treatment or	0 = No discussion 1 = Discussion

		procedure for a set amount of time with a pre-defined goal and plan related to the outcome at the end of the trial.	
Resuscitation and Intubation Preferences	Secondary	Preferences for, or limitations to, cardiopulmonary resuscitation and/or intubation.	0 = No documentation 1 = DNR/DNI 2 = No limitation 3 = DNR [Intubation is okay] 4 = DNI [Resuscitation is okay]
Enteral Feeding	Secondary	Mention of conversation with patient or family regarding preferences for, or limitations to feeding tubes.	0 = No discussion 1 = Limitation 2 = No limitation
Dialysis	Secondary	Mention of conversation with patient or family regarding about preferences for, or limitations to dialysis.	0 = No discussion 1 = Limitation 2 = No limitation

Domains	Keywords
Goals-of-Care Discussion	GOC, goals of care, family meeting, family discussion, patient goals, patient values, quality of life, prognostic discussions, illness understanding, serious illness conversation, serious illness discussion, advance care planning, advanced care planning, ACP, end of life, end-of-life, what matters most, poor prognosis, limited prognosis, prognosis, prognostic, dying, die, death, incurable, not curable, not curative, non-curable, non-curable, non-curative, non-curative, no cure, isn't a cure, is no cure, not reversible, non-reversible, treatments are palliative, treatment is palliative, palliation, extend life, extending life, life-extending, life extending, lengthening life, life-lengthening, life lengthening, life limiting, life-limiting, does not wish to know, does not want to know, hours to days, days to weeks, weeks to months, months to years, month left, months left, years left, year left, weeks left, week left, unfortunate, regrettably, I am afraid, frank discussion, frank conversation, honest discussion, honest conversation, difficult conversation, difficult discussion, out of options, no remaining options, no more therapy, no further treatment, end of life care, limit invasive procedures, natural death, molst, polst, advance care, advanced directive, advanced directives, advance directive, advance directives, life support, life prolonging, prolong life
Code Status Limitations	Intubation, resuscitation, vent, CPR, no intubation, no resuscitation, no CPR, declines CPR, do not intubate, do not resuscitate, DNR/DNI, DNR, DNI, DNRDNI, DNH, declines cardiopulmonary resuscitation, no cardiopulmonary resuscitation, declines intubation, no chest compressions, no compressions, no defibrillation, no mechanical intubation, refuses intubation, refuses CPR, DNAR, do not attempt resuscitation, no bipap, no NIPPV, comfort care, comfort approach, CMO, comfort directed care, prioritize comfort, comfort measures, code status, DNR OK to intubate, DNR/DNI/+LLST
Hospice	Hospice, bridge to hospice, home hospice, inpatient hospice, hospice house, hospice at home, GIP

Palliative Care	Palliative medicine, Palliative care, pall care, pal care, pallcare, palcare, PC, supportive care, pediatric palliative care (PPC)
Time Limited Trial	Time limited trial, limited trial, TLT
Resuscitation and Intubation Preferences	Full code, FC, full intubation, full resuscitation, Intubation, resuscitation, CPR, no intubation, no resuscitation, no CPR, declines CPR, do not intubate, do not resuscitate, DNR/DNI, DNR, DNI, declines intubation, declines cardiopulmonary resuscitation, no chest compressions, no compressions, no defibrillation, mechanical intubation, refuses intubation, refuses CPR, code status discussion, discussed code status, life support, DNAR, do not attempt resuscitation, allow natural death, code status
Enteral Feeding	Artificial nutrition, feeding tube, supplemental nutrition, nutrition support, PEG, dobhoff, G tube, gtube, g tube, J tube, jtube, j tube, GJ tube, gj tube, no artificial feeding, no feeding tube, declines feeding tube, refuses feeding tube, enteral feeding, gastrostomy tube, NG tube, nasogastric tube, OG tube, orogastric
Dialysis	Renal replacement therapy, hemodialysis, HD, iHD, CVVH, AVVH, hemodialysis not within goals, RRT, conservative management, medical management without dialysis, no dialysis, dialysis, peritoneal dialysis, PD

Support for NLP will also come from Yale University, a subcontract site in the grant though they will be IRB exempt since no human subjects research or identifiable data sharing will occur. The PI, Dr. Prasanna Ananth, will assist with validating keyword libraries for domains of interest (e.g., goals of care) across multiple study sites. She will also oversee natural language processing methods to evaluate the key study outcomes in clinical notes extracted from the electronic health record.

6.1.2 Primary and Secondary Outcomes

Child- and Parent-level data: Demographic: We will obtain key baseline patient demographic information from each health system's EHR. This will include: age, gender identity, race/ethnicity identity, primary language, religion. We will also use the **Social Deprivation Index (SDI)**, which is a composite measure of seven demographic characteristics collected in the American Community Survey (ACS): percent living in poverty, percent with less than 12 years of education, percent single-parent households, the percentage living in rented housing units, the percentage living in the overcrowded housing unit, percent of households without a car, and percentage nonemployed adults under 65 years of age.[178] The SDI measure was calculated at four geographic areas: county, census tract, aggregated Zip Code Tabulation Area (ZCTA), and Primary Care Service Area (PCSA). SDI scores are available for all counties, census tracts, ZCTA's, and PCSA's.[178] **Diagnoses:** The EHR will provide baseline information about diagnoses for children.

TABLE 4: Data Element	Purpose	EHR	Survey	Video Link
Demographic	Covariate (moderator)	X		
Disease type	Target sub-population identification, covariate	X		
GOC documentation	1^{o} outcome	X		

Preferences (CPR, etc.)	2º outcome	X		
Health Services Utilization	2º outcome	X		
Parent Surveys	2º outcome		X	
Intervention/Video use	Monitoring fidelity			X
Navigator activity	Monitoring fidelity		X	

GOC documentation (Primary Outcome): We will obtain the presence and content of GOC documentation from the EHR as assessed by documentation of GOC in the patient's notes using the NLP-assisted and human-confirmed program used in our prior work.

Preferences (Secondary Outcome): We will follow resuscitation preferences such as Full code, Do-not-resuscitate (DNR), Do-not-intubate (DNI), Do-not-hospitalize (DNH), and preferences around nutrition and hydration, and dialysis from the EHR. We will obtain the number and timing of palliative care visits and hospice use.

Additional pragmatic outcomes: Health services utilization: We will obtain the use, timing, and extent (instances or days of service) of ICU, CPR, ventilation, and hospice use, as well as burdensome interventions (CPR, intubation, tracheostomies and dialysis). **Intervention implementation:** We will obtain data about the use of the videos through the video links and video cards by monitoring video use by the navigators as well as remote viewings by parents.

Parent surveys: A subgroup of 136 randomly chosen parents in the intervention and control periods will have surveys assigned to them via REDCap. (This can be done via REDCap to assure random selection.) We will oversample parents of African American, Hispanic, and rural children as we have done for the larger trial. Given that African American, Hispanic, and rural children are at higher risk for dying in the hospital, we will over-sample our patients to include 45% (N=228) from under-represented communities. Parents will receive the survey at the time of randomization (i.e., initial visit), and then again after nine months (i.e., end of intervention or control period/cycle). We will contact parents by telephone after a week if the nine-month survey is not completed.

Parental Health Literacy Activities Test (PHLAT): We will use the PHLAT survey tool to measure health literacy during the baseline interview.[179] The PHLAT is a well-validated tool to assess parental health literacy and numeracy skills and has also been validated in Spanish-speaking parents (PHLAT Spanish).[179,180] Assessment of health literacy will occur at the baseline visit.

Parent Feeling Heard and Understood: We will ask 5 validated items regarding "feeling heard and understood" by the oncology team (e.g., I felt heard and understood by the oncology team. I felt my child was heard and understood. I felt the oncology team put my child's best interests first. I felt the oncology team saw my child as a person. I felt the oncology team understood what was important to my child).[161] Each statement is rated on a five-point Likert scale.

Parent Satisfaction with Healthcare: We will use two items from the Survey about Caring for Children with Cancer (SCCC) to assess satisfaction with healthcare.[35] The first assesses the care team's sensitivity to the child's needs (response options: a great deal, a lot, somewhat, a little, not at all). The second assesses quality of care delivered by the care team (response options: excellent, very good, good, fair, poor). *Both surveys are available and validated in Spanish.*

This survey for UH3 will be provided in a subsequent amendment following any UG3 phase refinements.

6.2 Ensuring Study and Intervention Fidelity

Ensuring Study and Intervention Fidelity: A fully pragmatic trial aims to maximize the "real world" character of the intervention implementation. It is also desirable to evaluate implementation

fidelity. Accordingly, we will monitor aspects of the intervention (Table 3) including number of interactions with parents over the course of the nine months of the intervention per cycle. This will include: length of each interaction, presence of additional family members, and, telephonic vs. televisual (each is automatically documented in the EHR with telehealth visits). Navigators will also use REDCap forms that template each aspect of the intervention. Accordingly, we will derive a measure of navigator implementation fidelity through REDCap based on a survey tool developed by Ang and colleagues specifically to assess fidelity of GOC interventions.[73] Navigator use of these forms will yield: length of contact; content addressed (GOC, code status, video use, other); contact with family and type (e.g., number of parents/family, friend); and, strategy used to assess patient comprehension.[74]

We will employ rigorous training procedures with in-person and remote training for navigators delivering the intervention. There will be continuous quality assurance by the investigative team and bi-weekly supervision calls with the Navigators. Bi-weekly supervision calls will include Drs. Volandes and Paasche-Orlow, who have trained over 1,000 clinicians in the GOC Video Intervention, and/or the PIs. This will involve review of challenging cases and role-playing. In addition to the bi-weekly individual calls, there will also be monthly group calls that will be supervised by Drs. Wolfe and Snaman covering GOC topics and case discussions. A key aspect of intervention fidelity will be review of audio-recorded calls. We will audio-record (with verbal parent consent) 5% of calls from each navigator over the course of the RWCT to enable us to assess the content of clinical encounters. The local site-PIs and overall site PI/Co-I/PM at MGH will review these audio-recorded interactions to provide feedback to navigators. This will be done with each navigator once during each of the three randomization cycles. In addition, themes from these feedback sessions will be brought anonymously to monthly group case-based navigator discussion sessions.

Table 3: Fidelity	Steps Taken to Ensure Fidelity	Fidelity Assessment
Navigator Training	- Use of a standard intervention training for navigators - Bi-weekly check-ins run by Drs. Volandes and Paasche-Orlow - Monthly remote Case-study sessions (PI led) - Retraining seminars via video conferencing with all navigators delivering the intervention	- Complete review of intervention guide - Completion of VitalTalk training session - Ongoing participation in Case-Study sessions - Assess pre- and post-knowledge that navigators acquired during retraining
Intervention Delivery	- Measure extent of exposure to the GOC video - Evaluation of REDCap documentation of content addressed during encounters	- Measure video exposure, document date of video viewing & playthrough rate - Site-PIs will review REDCap forms and audio-recorded visits (5%) to ensure adherence to content

Data Collection based on RE-AIM QuEST Framework: The RE-AIM framework is used to systematically assess key dimensions of intervention implementation to enable future dissemination in real-world clinical settings. RE-AIM developers emphasize the importance of collecting qualitative data to complement quantitative measures to comprehensively understand the contextual determinants of intervention implementation.[174-177] Throughout the project period, we will hold monthly video conferences with navigators and create a log describing the barriers and facilitators for implementation and adoption. Drs. Volandes and Eche are nationally recognized leaders in implementation science and qualitative data analysis. They will then use this feedback to further develop the semi-structured interview guides for the qualitative interviews with key informants. We will conduct qualitative interviews stratified by participating site. For each key informant group, we will interview 30 individuals (i.e., ten at each site). Specifically, we will conduct interviews with 1) 4 parents ; 2) 6 clinicians (4 primary oncology providers and two clinic leaders) at each site for a total of 30 key informants to identify facilitators and barriers to the

adoption, implementation, and maintenance of the GOC Video Intervention. We will collect the following data:
Reach: We will assess: 1) the number of eligible parents who were approached with the intervention; 2) number engaged, and characteristics of refusers and enrollees; and 3) reason for refusal to engage. We will also utilize the qualitative interviews with parents and clinicians to assess recruitment and retention facilitators and barriers and discuss how they can be addressed.
Effectiveness: We will evaluate effectiveness based on the comparative effectiveness of the video program to usual care on parent-reported outcomes. Additionally, we will analyze qualitative interviews of parents and clinicians about perceived effective features of the intervention.
Adoption: To examine adoption, we will assess parent participation rates (i.e., % of eligible parents viewing videos and telehealth sessions). We will also quantitatively summarize proportion of navigators completing the REDCap surveys for telehealth visits. We will solicit feedback during our qualitative interviews with navigators, clinicians, as well as clinic leaders related to implementation logistics and barriers to integration of these care models into clinical practice. In qualitative interviews with parents, we will focus on individual factors that may have affected their participation and their desire to engage with the intervention and whether it addressed their needs.
Implementation: We will assess implementation based on fidelity to the protocol and intervention delivery. We will review and quantitatively summarize data on documentation of GOC domains addressed during navigator encounters using the EHR. We will also review the REDCap surveys from navigators longitudinally to assess changes in the patterns of GOC domains addressed throughout the project period. In qualitative interviews with parents and clinicians, we will assess overall satisfaction with the intervention and focus on ideas for intervention modification and adaptation to maximize implementation into practice.
Maintenance: We will assess the comparative effectiveness of the intervention vs. usual care on care delivery to assess maintenance of intervention effects. During qualitative interviews with parents, we will explore whether modification to the intervention is needed. With clinicians, as well as clinic leaders, we will explore barriers and facilitators to the intervention maintenance and integration into standard practice. The team will continually review processes and surmount barriers to successful implementation of the intervention.

6.3 Alternative Treatments and End of Study Procedures

The alternative to participation in the pilot and development UG3 phase is not participating. Compared to standard care, involvement in the RCT (UH3) will involve answering surveys and participating in a semistructured interview. Additionally, those assigned to the intervention will be followed-up by the Navigator. Similarly to UG3, the alternative is not to participate. At end of study, control participants will be offered the Video component of the intervention also. No other ancillary care needs are expected. People who decline participation will continue to receive standard care without participation in the proposed research.

6.4 Study Incentives

UG3: Parent or provider participants will be offered a $50 gift card (for either focus group or interview participation).
UH3: Parents will be offered $20 for participation in the intervention, $20 for surveys (for the subset assigned this additional ask), and $50 for exit interviews. Providers (primary oncologists or clinic leaders) will be offered $50 for exit interviews.

Parent Advisors (N=3) will receive $100 gift card for their collaboration.

We believe the amount is a symbolic thank you for their time that will not be an undue influence on the decision to participate. Gift cards will be delivered by email or in-person.

7. Statistical Analysis

Given the randomized nature of the planned study, we will report our results according to CONSORT guidelines. We will record subject attrition and note all adverse events. We will employ the intent-to-treat principle in our comparative analyses between the intervention group and the control group. Our pre-specified hypothesis tests limited to three in number (2 from Aim 1 and 1 from Aim 2) and each will employ its own nominal significance level. Any *post hoc* analyses will employ adjustments for multiple hypothesis testing via a Bonferroni correction. In univariate analyses, we will examine the distribution of outcome variables, as well as the distributional characteristics of all other salient study variables. We will generate descriptive statistics (means, standard deviations, quantiles for continuous variables; counts and percentages for categorical variables) and schematic plots (box-and-whisker, quantile-quantile plots). We will compare the study groups in descriptive analyses to examine the balance in distributions on covariates achieved through randomization. We will compare the outcomes between study groups using chi-square tests for categorical outcomes and two-sample t tests for continuous outcomes. In addition, we will use multiple logistic or linear regression models to include randomization stratifying variables (site) and predictors of outcomes to increase the precision of effect estimates. These additional variables will be better defined in an amendment prior to the UH3 phase after year 2 involving randomization. SAS version 9.4 will be employed for all statistical analyses.

In addition to comparing the Intervention to Waitlist-Control arms, we will perform "dose-response" analyses within the intervention arm using the rate per month per patient of the number of telephone contacts made by the navigator as the measure of the level of treatment. We will first examine the distributional characteristics of this variable both overall and within each subgroup of interest (e.g., race/ethnic groups, rural/not rural) in order to determine the form of the variable that will produce the most valid and clinically relevant estimate of association with outcomes. This represents a quantitative assessment of fidelity. In addition, we will have a qualitative assessment of fidelity (described below).

Reporting dropout and missing data. Whenever a participant drops out of the study, we will document the specific reason for dropout, who decided that the participant would drop out, and whether the dropout involved intervention participation. If a participant withdraws from the intervention only, we will continue to collect data on all outcome measures. As noted above, all participants included will be accounted for in a CONSORT diagram. All post-randomization exclusions will be documented and accompanied by a rationale for exclusion.

9.1 Data analysis plan for quantitative outcomes

For UG3 acceptability, we will use proportions, means and SD, medians and IQR, or raw numbers as appropriate. We will report race/ethnicity and language profile of enrolled, refusals, and dropouts as well as reasons for refusals and dropout to assess the risk for selection bias and incorporate this information into our trial design.
For UH3, we will compare GOC documentation in 504 patients aged 0-12 with cancer randomly assigned to our GOC Video Intervention vs. Waitlist-Control.

9.2 Data analysis plan for qualitative outcomes

We will use a focused classic thematic analysis approach using grounded theory as the conceptual framework. Starting with a set of predefined codes (deductive coding) we will use inductive coding with further iterations to fit the data until saturation is reached.[109] Data coding will be performed by at least two people. Differences will be solved by team reflective discussion.

Analyses will be done using MaxQDA software.[110] Given their expertise in qualitative methods, Drs. Wolfe,and Snaman (site PI at DFCI) will oversee all aspects of focus group and exit interview analyses.

9.3 Power analysis

Statistical power and sample size. Our estimates for GOC documentation rate for Waitlist-Controls and Intervention for overall and each mutually exclusive subgroup are summarized in the table below. The study is planned for testing the interaction for *H1b*; therefore, it has more than sufficient power for *H1a*.

Table 1	Total N	Waitlist-Controls	Intervention	Power	MDD*
Overall	504	4.8%	27.3%	99%	7.2%
Non-Hispanic, non-rural White	276	6.5%	20.1%	80%	13.6%
Minority	228	2.6%	36.0%		10.3%
Non-Hispanic African American	76	2.6%	36.8%	91%	28.0%
Hispanic	76	2.6%	36.8%	91%	28.0%
Rural	76	2.6%	34.2%	86%	28.0%

***** minimally detectable difference with 80% power assuming alpha=0.05 for the overall group and alpha=0.0125 for the four mutually exclusive subgroups.

H1a Overall. We expect 4.8% documentation in the waitlist-control arm and 27.3% in the intervention arm. This is similar to our prior trials showing similar effects.[2,3] We will have 99% power to detect the difference of 22.5% which well exceeded the minimal detectable difference of 7.2% with 80% power and a two-sided alpha of 0.05.

H1a Subgroup-specific differences. We also examine power for subgroup-specific differences in GOC documentation at an alpha level of 0.0125 to account for multiple comparisons hypothesis testing. As shown in the Table, all 4 subgroups will have 80% or higher power for the comparison between the two study arms.

H1b Heterogeneity-of-treatment effects. We expect the intervention effect to be a 13.6% increase (from 6.5% to 20.1%) in GOC documentation among non-Hispanic, non-rural Whites compared to a 33.3% increase (from 2.6% to 36%) among all other groups combined. This is similar to our prior trials showing greater effect in subgroups.[2-4] The study will have 80% or higher power to detect the difference-in-differences with a two-sided alpha of 0.1.

In summary, we expect that we will have sufficient statistical power to detect clinically meaningful effects of the GOC intervention for our primary outcome and in subgroup-specific analyses.

8. Risks and Discomforts

8.1 Potential Risks

There are no known risks for any subjects participating in this study beyond the emotional reaction that some questions might cause and the erroneous sharing of protected health information. There is potential benefit to subjects participating in some aspects of this study.

The experience of the intervention could serve to improve parents' understanding of medical care for their children and improve communication for GOC and self-determination.

With the randomized waitlist-controlled trial we can curate the list of people who will be assigned to get the intervention at the start of each of our three nine-month cycles to either Intervention or Waitlist-Controls. We have pre-specified the target gender, racial and ethnic distribution of children in each health system who will be in this trial, that is: 50% Women, 15% Hispanic, 15% Non-Hispanic Black, 15% non-Hispanic rural, and 55% Non-Hispanic White (see Planned Enrollment Table). The randomized waitlist trial method enables these prespecified design choices. Further, we will strive for the 5% audiotaped sample of navigator interactions with parents will reflect the demographic distribution of the study population.

We do not foresee a significant challenge with ensuring follow-up as all study activities are completed either passively by patients (i.e., via EHR), through consent in a single recorded episode (i.e., the interaction between the navigator and the parent), or through consent in a single qualitative interview. For the subgroup of parents that will be surveyed, we expect 5% of parents not to complete the surveys and we have chosen an appropriate number of parents to survey to have the appropriate powered analyses.

To date, most randomized trials conducted with children with cancer and their parents were evaluated under ideal circumstances (i.e., explanatory trials). Pragmatic trials, which intend to determine the effects of interventions under usual conditions, are a next critical step in research involving children with cancer and their parents. Based on the Pragmatic–Explanatory Continuum Indicator Summary Tool, the rationale for the proposed pragmatic trial is compelling and we will abide by the extended CONSORT recommendations for pragmatic trials.[63-65] Our three participating health care systems will engage parents of children with cancer in goals of care as a standard of care. Thus, the proposed trial is designed in a manner that fits the ethical and clinical parameters of outpatient-based palliative care and will provide data to understand the impact of our proposed intervention.

While many large-scale pragmatic trials are implemented with a stepped-wedge design, this trial is designed as a pragmatic randomized waitlist-controlled trial. We can do the randomized waitlist-controlled trial design as our intervention model and clinical context allow for this approach, which has several notable advantages over the stepped-wedge design. This design is practical for the circumstances of the current proposal and provides the full research rigor of an RCT that is randomized at the patient level. This is far superior to randomization at a group level (e.g., provider, clinic). The stepped-wedge design is much more susceptible to the influence of secular trends and would require a much larger patient sample size to evaluate the same outcomes. Similarly, in the context of a stepped-wedge design pre-specified subgroup designation for oversampling is not feasible. Accordingly, the waitlist design is more efficient, more rigorous, and more amenable to research regarding demographic subgroups than a stepped-wedge design. Both study designs share the benefit of being able to eventually provide the intervention to all people in the target population; this is a trial design feature that was preferred by our clinical partners.

One of the principal risks of participating in this research is the possibility of loss of confidentiality. The likelihood of these risks is very low. The questions that could cause emotional responses are clearly within the scope of normal clinical care. In the unexpected event of significant psychological distress due to participation, 1) Participants will be reminded that participation is voluntary and that they may stop participating at any time for any reason. 2) If a participant

experiences distress, additional psychological support will be offered to the participant at that time. Each pediatric cancer center has a system of psychosocial support for patients and family members, and participants will be referred to these existing supports should they experience distress and require additional support. 3) The site-PI will also be notified of any participant who experiences distress and be responsible for coordinating psychosocial referrals and ensuring follow-up. The MPIs will be notified within one business day from the time the site-PI is notified

Given the extensive safeguards in place to protect subject's confidentiality, the risk of serious breaches is extremely low.

8.2 Protections to Minimize Risks

Overall, this study presents no more than minimal risk. None of the risks are expected to be significant. The following safeguards to minimize such risks will be in place:

Subjects will be informed that they can refuse to answer any question and may choose to stop participating at any time. In addition, if at any time participants report feeling distressed because of study participation, a referral to a psychosocial clinician will be offered. Should a participant become distressed because of completing study they can stop at any time. The RA will offer to phone them back the next day to see how they are managing. If deemed necessary, the RA may suggest to the parent that they contact their primary healthcare provider. In the event the parent does not have a primary healthcare provider, the RA will offer the parent a list of appropriate referral sources if they wish. We will schedule all interviews at the convenience of parents and will administer them using their preferred method when possible (phone, video conference, in-person). Notably, we have used similar procedures during prior trials and have not had anyone ask for or require added psychosocial support.

Protections against risk from participation

Subjects in the usual care arm will receive routine care and as such if a child presents with persistent distress, they will be cared for through typical mechanisms. During the consent process all participants will be counseled to follow-up with their usual providers if they are concerned about distress. For subjects in the intervention, GOC communication will be funneled to the primary oncology provider as appropriate and the pediatric palliative care (PPC) team may be referred when needed.

Confidentiality safeguards

Confidentiality safeguards include the use of unique study alpha-numeric code identifiers for all subjects. In addition to what was described in section previously, the REDCap system validates the identity of trusted partners using digital certificates and keep a full audit trail of all transactions. Management of PHI: PHI data will be collected directly through the pool list and REDCap. Most identifiers (names, emails, addresses) will be stored in separate protected tables accessible only to the local study team, system managers, and the PM. Once the database is locked, these identifiers will be destroyed (only those identifiers needed for analysis will remain in the final database). For subjects deemed ineligible (pool list and REDCap data), all PHI obtained for screening purposes will be destroyed as soon as possible. No study information will be released to any other party except to MGB or site IRBs and local regulatory authorities, if requested.
Any breach of confidentiality will be subject to a root cause analysis and preventive measures taken as appropriate. All these procedures are likely to be effective based on our prior research experience.

Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☒ Additional privacy and/or confidentiality protections

Each site will maintain and adhere to the process and procedures for the protection of human subjects and protected health information (PHI) for their covered entities. All data collected by the RAs will be stored in protected files on servers behind institution firewalls. Participant identifiers will be kept in separate password protected files and a third linking file will be maintained. The linking file will also be password protected, access will be minimized, and a logging feature will be used to identify each user and instance of use. Only the minimum amount of PHI necessary will be collected from study participants. Data from each of the clinical sites will be transmitted via secure, institutionally approved methods to MGH for data management and qualitative analyses. The MGH Research team, under the direction of Dr. Wolfe, will produce written transcripts of the videos and may also assist in coding the transcripts and grouping/summarizing the codes into themes for analysis using MAXQDA software.

All information in the REDCAP database will be indexed by subject identifier, so that even if the database server is compromised subjects cannot be identified, thus maintaining the privacy of their information. Also, assurance of confidentiality of information will be made to all subjects. Data will be handled with the same confidentiality accorded to patients' medical records. Specific procedures protecting subject confidentiality will be as follows:
1. ID number only will be placed on electronic (or paper) study forms or records on which data are collected and/or stored.
2. Access to data files will be secured with a password-filing system (that logs entry) and is restricted to authorized staff only.
3. Necessary hard-copy records containing study data of any type will be kept in locked files.
4. Master lists linking subject information with ID number will be numbered consecutively and prepared before data collection (to ensure accurate accounting). These lists will be kept locked, in duplicate, with access only by the PIs and the other investigators.
5. All project staff will sign an oath of confidentiality to ensure their understanding of the terms of confidentiality required. They will be trained in specific procedures to ensure confidentiality.
6. Sign-out procedures for all access to data files will be strictly enforced.
7. All reports and publications will preserve participants anonymity.

We will use of Dropbox for Business (DBFB) as the central repository for storing all of the fixed and NLP data that the sites send to us which will allow our data team to store data, documentation about data and code used to analyze the data in a platform that best compliments their workflow. DBFB is HIPAA compliant, approved for use by all sites, and will only be accessed by study staff.

To carry out the study it will be necessary to collect and store some personal health information (PHI) including:

- Contact information (names, addresses, email addresses, and phone numbers) necessary to identify subjects initially and ask for consent, send the mail surveys throughout the study. Medical record numbers needed to verify eligibility and abstract medical information.
- Patient's / Parent's dates of birth, to calculate their age.

These data will be collected during the recruitment process in the pool list and REDCap. All research staff collecting PHI will have HIPAA Certification and the training mandated by the Institutional Review Board. Confidentiality safeguards have been thoroughly described in sections 10 (Data Management Plan) and 8.2 (Protection against risks).

Additional security features of the REDCap include:

- secure user authentication, password encryption in both front and back ends, and role-based access controls that prevents users from accessing data that they are not authorized to see (e.g. patients cannot see other patients' data and local RAs, Project Manager, or PIs cannot see other sites information; only authorized technical personnel who provide support can have access to each of the system's back end data).
- validation of the identity of trusted partners using digital certificates and full audit trail of all transactions.

All study desktops and hand-held computers will be within the sites firewall. All participating centers' information technology groups adhere to policies and practices under the HIPAA regulations creating a very tight computing environment, which makes it difficult for individuals external to the study to access the databases.
Because of the safeguards in place, we believe that subjects' confidentiality will not be affected, and the risk of serious breaches is extremely low.

9. Benefits

Potential benefits of the research to research subjects and others: The risks to subjects are reasonable in relation to anticipated benefits and in relation to the importance of the knowledge expected to result from the clinical trial. The research team has hypothesized a greater proportion of intervention participants will have documentation of GOC discussions (primary outcome) in the electronic health record. However, there may be no benefits to subjects from participation in the proposed research. Society, medical science and the health care system may benefit from the information obtained in the research on improving care for patients with advanced illnesses and limited prognosis.
Data collected as part of the study will be made available to investigators who are part of the proposed study team or who join the study team. In addition, data will be shared with other investigators via the Open Science Framework repository (or other venue as directed by NCI) in accordance with NCI policy. This sharing and additional analyses promise to allow exploration of additional scientific questions.

Why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others: Anticipated benefits exist for individual subjects as the intervention may improve care for patients. Specifically, there is a potential benefit to children to receive medical care that is concordant with their (parents') goals and wishes.

Importance of the knowledge to be gained as a result of the proposed research and why the risks are reasonable in relation to the importance of the knowledge that reasonably may be expected to result: Determining the use of video decision support tools for more informed decision-making for parents and children with cancer is an important area of research where there are currently very few data. The minor risk for the subjects in this study may be considered to be counterbalanced by the knowledge gained. The results gleaned from the study are intended to identify factors that promote medical care for cancer that are consistent with the individual preferences of parents. The use of video can be applied to design future interventions aimed at improving communication between clinicians and parents. The risks to subjects in this study are reasonable in relation to the importance of the knowledge that is expected to result. Thus, the risk/benefit balance for this study appears favorable.

10. Data Management Plan

Data management will occur at all sites and data collected will flow to the lead site, MGB, for analysis and monitoring. As the Study Data Center (SDC), this will be covered by subcontract and data use agreements necessary. MGB will be responsible together with the study Data and Safety Monitoring Board (DSMB) for providing a specific data collection and monitoring system, including the design of the Data Management Plan, Standard Operating Procedures (SOPs), Data Validation Plan, study data collection and completion guidelines for investigators, supervising data collection procedures, assuring maintenance of high quality databases, and arranging an efficient and safe transfer of non-electronic study data, in compliance with Good Clinical Practices (GCPs). RAs and site PIs will be responsible for the local data centers (LDC) and will communicate with the SDC on a routine basis. RAs will be trained in data management procedures, GCPs, and human subjects protection before starting enrollment. All sites adhere to policies and practices under the HIPAA regulations creating a very secure computing environment.

Each subject (child and parent) will be assigned a unique study identification number. Hard copy surveys will be stored in locked file cabinets and labeled with study ID rather than patient identifiers. Survey data will be entered into REDCap. Most data collection will be done using password protected Excel and REDCap systems on protected servers. (Minimally identified datasets from these sources will be shared with MGH through Dropbox Business as described.) All other source documents, audio files and transcripts, and survey data, will be created as or converted to electronic format and stored on HIPAA compliant cloud servers, accessible only through use of a unique password. In the case of audio recordings, participants' names will not be directly linked in any way with the recordings and all personal references will be removed when the tapes are transcribed. Excel files are stored in RA's computers or site's network and accessible only to the study team. RAs will generate de-identified reports that will be shared with the lead site. Data user and confidentiality agreements between sites are in place allowing data to flow to MGH. Data will be sent by secure file transfer as allowable per site regulations and meeting GCP and HIPAA compliance standards (see Section 7.2.3. Confidentiality, for more details).

We will track enrollment, retention, and data completion. Whenever an inconsistency is detected, it will be solved by the site RA and validated in the database by the PM at the SDC. The PM will audit inclusion, recruitment, and medical record abstraction processes by comparing inclusion/eligibility forms, and data abstracted from charts against medical records on a random sample of 10% of all screened subjects.

Access to the data will be limited to the PI and designated study personnel at the above mentioned sites on a "need to know" basis and covered by Data User Agreements (DUA). The datasets may contain some identifiers such as dates of birth or death, zip code, or diagnosis needed for analysis (specified in the corresponding DUA) and will be shared through HIPAA compliant cloud servers (Dropbox Business). The SDC will oversee intra-study data sharing processes, with input from the DSMB. While on study, local PIs will have access to their site data and to summary reports of trial progress.

At the end of the study, and after a comprehensive quality check and assurance, the final data validation will be run. If there are no inconsistencies, a pre-lock checklist will be used and completion of all data management activities will be confirmed. Once the approval for locking is obtained from all key project stakeholders, including the study statistician, the database will be

locked and clean data will be extracted for statistical analysis. The database will not be changed in any manner after locking. Once the database is consolidated, all investigators that are interested in leading a particular analysis, will be given access to the final password-protected de-identified (or minimally identified) data sets. Out of study investigators may be allowed access to the datasets after a formal analysis proposal is approved by the steering committee. This protocol operates under the single IRB model and as such, all sites will cede the review to the lead site and rely upon the DFCI IRB, as the MGH IRB of record. The study team will prepare and submit a "requested to rely" form for the DFCI IRB to serve as the IRB of record for this project. Ancillary reviews may still be completed by local IRBs as required.

10.1 Monitoring and Quality Assurance

10.1.1 Adverse event criteria and Reporting Procedures

Any adverse events related to study procedures will be initially monitored by the study team (using the standard site study adverse event form / log), reviewed in site team meetings, and escalated as required. (The project manager, co-Investigators, MPIs and statistician will review aggregate data regarding adverse events in a blinded manner when at all possible.)

Safety monitoring for the study will be overseen by the Safety Monitoring Committee (SDC) and the Data Safety Monitoring Board (DSMB). Information on all potential types of adverse events will be collected at all assessment points and recorded on standard forms (major violation or minor deviation logs). In preparation for their quarterly feedback, the DSMB will analyze the rates of adverse events and evaluate the possibility that the intervention is causing harm. If at any point there is a severe adverse event (such as a death, suicide or serious consideration of suicide, or a change in mental health requiring hospitalization, that is felt to be related to the study), we will suspend study activities and try to determine if there is any link between study procedures and the adverse event and determine if any modification is advised or if the study should be stopped. If an adverse event is detected, the PI will be responsible for promptly reporting it consistent with Mass General Brigham, local sites, and funding agency policies.

The MPIs and the DSMB are responsible for monitoring the proposed clinical trial as supervised by their respective IRBs. The DSMB will further monitor the study to review any breaches in protocol or confidentiality or other adverse events. To evaluate safety in the randomized trial and to review any potential breaches in protocol or confidentiality, and other adverse effects, the DSMB will have planned meetings every six months and additional meetings if needed. Additional meetings will be arranged if required based on a need to review information about events or issues that may arise, such as an unexpected number or severity of adverse events. For safety monitoring, discussion will take place on whether or not reported incidents are unanticipated and/or place subjects or others at greater risk of harm and if protocols or consent processes need to be modified. Unanticipated incidents will be reported to the IRB and/or funding agency promptly.

We will follow guidelines set forth by each site's IRB regarding "unanticipated problems" and "adverse events." Unanticipated problems are defined at MGH/Dana-Farber as events that are 1) unanticipated, 2) related to the research, and 3) a new risk or serious event (e.g., death, life threatening, hospitalization, disability, birth defect, or requires medical or surgical intervention to prevent any of those from happening). Unanticipated problems will be reported within two days of the investigator learning of the incident as well as to the IRB. The report will explain why the

incident is considered an unanticipated problem and how the protocol will be modified in accordance with a corrective action plan. Incidents that do not meet all three of the criteria noted above will be considered adverse events or serious adverse events but not unanticipated problems. In these cases, they will be reported to the IRB at the time of the annual progress report. The report will provide information on cumulative incidents, and if in total the events suggest that subjects or others are at greater risk than initially determined, then the investigators will address whether or not the consent form needs to be changed.

10.1.2 Data and Safety Monitoring Plan

As the sIRB hub of this project, Dana-Farber Cancer Institute IRB will serve as the hub for all ethical and regulatory processes for the protection of human subjects and privacy protections.

A study scientific Data Safety and Monitoring Board (DSMB) consisting of scientists who are not affiliated with any of the study sites will be convened at the beginning of the study, via several conference calls / videoconferencing, to provide input and guidance on the study evaluation and intervention protocols, including quality assurance and safety issues related to the protocols, as well as data handling activities. They will also provide input and feedback every six months, via e-mail and conference calls, related to study recruitment, study eligibility determination issues, consent processes, data completion rates, and adverse events. Well-respected scientists with clinical trial research experience in decision making or related areas with children with cancer and are familiar with all of the areas noted above will be selected.

We have created a list of DSMB Advisors with expertise in pediatric cancer care, palliative care, pragmatic trials, implementation science, and biostatistics. DSMB Advisors include: Pamela S. Hinds, RN, PhD, Executive Director of the Department of Nursing Science, Professional Practice, and Quality, the William and Joanne Conway Endowed Chair in Nursing Research, and the Research Integrity Officer at Children's National Health System in Washington, D.C., and a Professor of Pediatrics at the George Washington University, School of Medicine and Health Sciences in Washington, D.C. Dr. Hinds is an international leader in pediatric cancer care, GOC discussions, palliative care, and quality improvement; Dr. Tammy I Kang, MD, MDCE, Professor of Pediatrics, Palliative Care, Baylor College of Medicine and inaugural Division Chief of Palliative Care at Texas Children’s Hospital and board member with the American Academy of Hospice and Palliative Medicine. Dr. Kang is an international leader in pediatric palliative care program development, implementation, and evaluation; Rachel Thienprayoon, MD, MSCS Associate Professor of Anesthesia, University of Cincinnati, Medical Director of StarShine Hospice and Palliative Care. Dr. Thienprayoon is an expert in pediatric palliative care quality improvement and a member of the board of directors of the Palliative Care Quality Collaborative and the Chair of the Pediatric Palliative Care Taskforce of the National Coalition of Hospice and Palliative Care; Liliana Orellana, PhD, Professor of Biostatistics, Deakin University. Dr. Orellana has served as the lead biostatistician on the PediQUEST Trials, evaluating primary and specialty palliative care interventions in children with cancer.

In preparation for their feedback, the DSMB will compile the rates of adverse events and evaluate the possibility that the intervention is causing harm. Project staff will provide data to the DSMB. The DSMB will be free to determine the need to stop the protocol due to harm or early proven benefit (or futility) - based on examination of adverse events or a proven statistically significant difference between intervention and control as determined by a blinded between arm analysis done at predefined intervals. The DSMB will independently confirm all parameters of

early stopping rules as well as all other procedures as part of initiating their DSMB Charter. At minimum, in each report it will be recommended that the DSMB will examine rates of adverse events and evaluate a preset stopping rule for a statistically significant (one sided P<0.05) higher count of adverse events (i.e., emotional distress) in the intervention group. The study team will be blinded to the results. Further, the study team, including the project manager, statistician, co-Investigators and research assistants, led by the study MPIs, will report to the DSMB regarding the progress of the research, including periodic assessments of data quality, subject recruitment, accrual, and factors external to the study when interpreting the data, such as scientific developments or the new availability of proven clinical services that could have an impact on the safety of the subjects, the performance of the study or the ethics of the study.

Meetings of the DSMB will have open-session and closed-session periods. The MPIs and the co-Investigators will attend the open portion of these meetings but will not vote and will not participate in the closed portion of the meetings. Blinded reports will be generated for these sessions. The study statistician, Dr. Yuchiao Chang will be designated to remain at the start of the closed session if unblinding will be requested. Dr. Chang has no contact with study subjects and is well versed in the ethical requirements of working with and between a study team and a DSMB. Following each meeting, the DSMB will make recommendations on continuation, modification, or termination of the studies. Within three months of the start of funding we will constitute the DSMB, name the members and establish its charter. We have had success with these DSMB methods in pervious trials.

Risk assessment

Participation in the proposed research is “minimal risk” which is defined as “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests,” (from 45 CFR 46.102(i)), with the exception of the risk of loss of confidentiality. This risk (as well as the other risks) is addressed above. The risk of breach of confidentiality is best addressed by appropriate study procedures; however, the MPIs will be responsible for assuring that study procedures are adhered to regarding data security, transfer, and communications in tracking subjects by meeting regularly with study staff, reviewing procedures and performing quality control reviews of study forms. Our assessment that the proposed project be regarded as minimal risk is based on over a decade of research experience relating to decision making and has been affirmed by 16 different institutional review boards that have been involved with various previous and current multi-site trials. If the institutional review board for the current proposal arrives at a different assessment, we would certainly adapt our approach accordingly.

Data Management and Security to Protect Privacy

The **Data Management Plan** (**DMP**) employed in this clinical trial has been developed in other studies and assures high quality forms, monitors data quality, and tracks and links the multiple data sources. Data are linked and entered using multiple checks. The DMP develops data collection forms, designs the database management system for data entered and for subject tracking, implements procedures for quality control, and provides statistical programming and collaborates in report writing and presentation of study results.

Databases are located on secure, password-protected servers, behind the MGH/Dana-Farber firewalls. The web and database servers use Secure Socket Layering (SSL) to ensure data

security and confidentiality. Servers incorporate RAID hard drives for data redundancy. A separate web server dedicated for Cold Fusion applications is also available. Specifically, the policies for computer systems security implemented at MGH/Dana-Farber are as follows:

- Provide physical security of data. The server resides in the same building as the Medical Center Office of Information Technology (OIT) servers. The lobby of the building in which the systems reside is under the security purview of the General Services Security Office and is under surveillance. All central systems are physically secured behind two card-access doors with access to the primary door restricted to key personnel in the OIT. Access through the primary door is also protected by a keypad alarm system that is tied directly into the on-site central emergency response security control center. Written policies exist for contingencies to provide access to the room to those not explicitly authorized.

- Provide virtual security via connectivity. Internal access to all systems is done via Microsoft Challenge Handshake Authentication Protocol. With the exception of internet provider-based services, external client access must first gain access to the internal network before connecting to the systems. This connection is initiated via a Virtual Private Network connection using Point-to-Point Tunneling Protocol or through the University's modem pool which require Kerberos authentication. All web-based mail is encrypted with high-encryption domestic SSL.

All data are protected with disaster recovery via several methods:

- Hardware redundancy: Several stages of redundancy exist at the hardware level to minimize failure: Dual-redundant power supplies exist on each disk array; hot-spare disk is configured to automatically self-heal in the event of a disk failure in the array; emergency power generators ensure a 100% electrical uptime; and uninterrupted power supplies present the systems with conditioned steady-state power.

- Data backup: Backups are completed daily over the network using both on-site and off-site disk-based backup devices.

- Data Security: All data are stored on servers that are password protected. To protect against security breaches, data will be electronically encrypted so that only the intended recipient can decode.

Data collection forms. The DMP will support the research team in designing, piloting, and implementing data collection forms by ensuring that the data fields are unambiguous, and the systems for recording information function smoothly.

Data Management Manual of Operations. The DMP includes a Manual of Operations to document all data collection and management procedures for the study.

Quality control procedures for data collection and data entry. Quality control measures are essential in any research effort. The quality control measures implemented by the data management team and described in the manual of operations include detailed and unambiguous specifications for completion of each of the data collection forms, including rules for coding skipped questions, missing data, etc., and interim incremental data reviews to assess for variation in the data. Throughout the conduct of the study, the data management team will

be available to the research personnel by email, tele- and web-conference to clarify questions regarding the data collection.

Quality control (QC). The Project Manager will monitor the quality of the data throughout the study, maintaining vigilance for outliers and other "blips" in precision, and, when found, exert prompt corrective action. QC measures will be: Detailed and unambiguous specifications for completion of study data; check for out-of-range codes and internal inconsistencies; data quality; interim analyses comparing data collectors to determine variations.

Creation of analytic datasets for statistical programming. For qualitative data, Drs. Snaman and Eche will be responsible for supervising the coding, analyses, any consensus processes needed, and maintaining the data. Dr. Lindvall's data teams will be responsible for cleaning the quantitative datasets, construction of the analytical variables, and writing the computer code to format and label each variable in the datasets. Documentation will be developed that will include data dictionaries defining the field names, location, and formats of all variables, the data collection forms, coding manuals, and documentation for computed variables and scale construction. Data will be cleaned in "batches" and cleaned batches appended to the master database. Statistical summaries will be provided.

11. Return of Results

Analysis of the trial results will include the full sample, unless scientifically justified. The Steering Committee will make recommendations regarding when and what material should be submitted for publication. Each paper will be reviewed and approved by the SC members prior to submission. The SC will work to reduce the interval between end of data collection and release of the study results. Publications will take place after each phase of the study. We expect to take about 4 to 6 months to compile and submit the main papers. Study results will be released to the participating physicians and referring physicians through publications in peer-reviewed journals, congress abstracts, and oral presentations. We will design lay summary materials to disseminate results among study participants (through the email addresses provided for the study) and the general public.
Participants in the research can opt in to being contacted later with the eventual findings and publications of the study. This will be documented at the time of participation (where consent is waived) or consent.

12. Long-term Data Storage

Data stored on the DFCI server will reside there only for the periods they are required to be there for study usage. After analysis is complete we will keep our datasets stored for the required seven years and de-identified data indefinitely, which will reside at MGH in long-serve storage.

13. ClinicalTrials.gov Requirement

This application includes an applicable clinical trial that requires registration (e.g., at ClinicalTrials.gov) as the FDA Amendments Act (FDAAA) mandates registration and results reporting. Registration will be completed prior to enrolling the first participant in the clinical trial. The MPIs will be responsible for registration. As the trial has not yet been funded, it has not yet been registered and as such an NCT number is not available.

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☒ Describe number and types of (i.e., qualifications of) members:
See section 10.2

☒ Describe planned frequency of meetings:
See section 10.2

☒ DMC/DSMB reports with no findings (i.e., “continue without modifications”) will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.