DF/HCC NON-CLINICAL PROTOCOL TEMPLATE
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PROTOCOL TITLE: Improving Patient and Caregiver Understanding of Risks and Benefits of Immunotherapy for Advanced Cancer

***Sponsor-Investigator:**
Laura A. Petrillo, MD
Massachusetts General Hospital
lpetrillo2@mgh.harvard.edu

***Principal Investigators (PI):**
Laura A. Petrillo, MD
Massachusetts General Hospital
lpetrillo2@mgh.harvard.edu

Note: The PI acting as the regulatory sponsor is known as the Sponsor-Investigator. In addition, each participating site must have a PI who is responsible for study conduct and oversight at their institution.

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Table of Contents

1.0 Objectives* 3
2.0 Background* 3
3.0 Inclusion and Exclusion Criteria* 6
4.0 Study-Wide Number of Subjects* 7
5.0 Study-Wide Recruitment Methods* 8
6.0 Multi-Site Research* 8
7.0 Study Timelines* 8
8.0 Study Endpoints* 8
9.0 Procedures Involved* 8
10.0 Data and Specimen Banking* 11
11.0 Data Management* and Confidentiality 11
12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects* 13
13.0 Withdrawal of Subjects* 14
14.0 Risks to Subjects* 14
15.0 Potential Benefits to Subjects* 15
16.0 Vulnerable Populations* 15
17.0 Community-Based Participatory Research* 15
18.0 Sharing of Results with Subjects* 16
19.0 Setting 16
20.0 Resources Available 16
21.0 Prior Approvals 18
22.0 Recruitment Methods 18
23.0 Local Number of Subjects 18
24.0 Provisions to Protect the Privacy Interests of Subjects 19
25.0 Compensation for Research-Related Injury 19
26.0 Economic Burden to Subjects 19
27.0 Consent Process 20
28.0 Process to Document Consent in Writing 21
29.0 Drugs or Devices 21
30.0 Appendices 21

1.0 Objectives*

1.1 The purpose of this study is to refine and pilot test an intervention developed to educate and support patients receiving immunotherapy for advanced cancer. The intervention is an educational video and question prompt list (QPL) to promote communication between patients, caregivers, and the oncology team about the risks and benefits of immunotherapy. The aims are:

Aim 1. To refine an intervention for patients with advanced cancer who are initiating treatment with immunotherapy and their caregivers, to educate them about the possible outcomes of treatment and to enhance communication with their oncology team. (Study Part 1).

Aim 2. To determine the feasibility of conducting a randomized trial of our intervention versus usual care in patients with advanced cancer initiating immunotherapy and their caregivers. (Study Part 2).

Aim 3. To evaluate the preliminary efficacy of the intervention to improve patient and caregiver knowledge about immunotherapy, enhance patient-clinician communication, and reduce patient and caregiver anxiety in a sample of patients with advanced cancer initiating immunotherapy and their caregivers. (Study Part 2).

1.2 We hypothesize that at least 70% of eligible patients will enroll in the study, and at least 80% of intervention participants will watch the video and review the QPL. Further, we hypothesize that patients assigned to the intervention and their caregivers will report greater knowledge of the possible outcomes of immunotherapy, communicate more frequently with their oncologist about potential risks and benefits of immunotherapy, and experience lower situational anxiety compared to those receiving usual care.

2.0 Background*

2.1 **Immunotherapy is a new paradigm of cancer treatment.** Immunotherapy, specifically a class of medications called immune checkpoint inhibitors (ICI), has transformed the landscape of therapeutic options for patients with poor-prognosis cancers, including melanoma and lung cancer. The cytotoxic T-lymphocyte associated antigen 4 inhibitor ipilimumab ended a bleak era for advanced melanoma by improving survival and becoming the first Food and Drug Administration (FDA)-approved ICI.[14] The programmed death 1 receptor (PD-1) inhibitors, pembrolizumab and nivolumab, subsequently gained FDA approval on the basis of superior survival outcomes in advanced melanoma in 2014.[15,17] Inhibitors of PD-1 and its ligand, PD-L1, also improve survival for patients with metastatic non-small cell lung cancer (NSCLC).[18,20] Perhaps the most exciting and promising aspect of ICI is the plateau in survival curves that emerges at two to three years of follow-up in patients with melanoma, suggestive of durable survival.[4] A subset of patients treated with ipilimumab have had prolonged responses that may last as long as 10 years or more.[7] The dramatic and sustained success of immune checkpoint inhibitors in a subset of patients with metastatic melanoma has strengthened support for the conjecture among researchers that immunotherapy may be curative.[21,22] As immunotherapy becomes first-line treatment for an increasing number of indications, it is quickly becoming a mainstay of cancer treatment, and a beacon of hope for patients and families.

Immune checkpoint inhibitors also bring new challenges: heterogeneous responses and toxicity. Not all patients experience the benefits of ICI, and those whose tumors do not respond unfortunately face a similarly poor survival as in the era before immunotherapy. Response rates with single-agent nivolumab or pembrolizumab in melanoma range from 36-40%.[2,16,23] Combination therapy with nivolumab and ipilimumab in advanced melanoma results in significantly higher response at 58%, but the proportion of patients experiencing toxicity is also greater, with 59% experiencing grade 3 or 4 toxicity, and 36% stopping treatment due to toxicity.[2] Among patients with metastatic NSCLC, objective response rates to single agent ICI range from 14-20%.[18,20,24,25] The response rate among patients treated with combination immunotherapy and chemotherapy is 48%, and 85% have either a response or stable disease, though 67% of patients experience grade 3 or higher toxicity.[26] The biomarker PDL1 is used to guide treatment for some cancer types, including NSCLC, but is an imperfect predictor of response, and oncologists thus must prepare patients and their caregivers for very different possible outcomes.[27,28] For patients and families, the experience of a poor response to immunotherapy, after hearing hopeful messages about its "game-changing" benefits, can be profoundly disappointing.[5]

Toxicity is another challenge that patients treated with immunotherapy face. Though ICI are generally well tolerated, toxicities may affect any organ system and lead to serious adverse effects, resulting in hospitalization or requiring lifelong treatment.[6,7,29] Rarely, immunotherapy toxicity can be fatal.[29,33] Moreover, toxicity may emerge several months after initiating treatment, requiring ongoing awareness and vigilance on the part of patients and clinicians.[6,29] Little evidence exists to predict toxicity risk. The risk of toxicity therefore adds an additional layer of complexity and uncertainty to patients' experience of immunotherapy. Patients are often unprepared for the possibility of toxicity. The goal of improving awareness of toxicity risk is not to change patients' decision to proceed with treatment, but rather to increase their surveillance for side effects in order to promote prompt evaluation, and prepare them for the possibility of needing to hold or stop treatment due to adverse events.[34]

Patients and caregivers require education about the goals, risks, and benefits of treatment. While patients' and caregivers' informational needs vary by individual, multiple studies have demonstrated that they generally want to be well informed about the risks, benefits, and goals of their cancer treatment.[35,38] Further, having an accurate understanding of the likely outcome of illness increases the likelihood that patients will receive care that is consistent with their preferences.[39,40] Despite their preferences for information, most patients with metastatic cancer misperceive the role of chemotherapy and believe that it may cure their cancer.[41,43] Caregivers of adults with incurable cancer frequently report not learning about their loved one's prognosis until their last month of life, or at all, though they also have difficulty comprehending prognostic information from oncologists.[44] The range of possible outcomes with immune checkpoint inhibitors makes understanding the goal of treatment and likelihood of benefit even more difficult, especially given the potential for long-term responses and the possibility that immunotherapy may not be safe to administer due to toxicities. Direct-to-consumer advertising and optimistic counseling by oncologists may further affect patient and caregiver expectations.[45,46] Patients need clear communication about their clinical outlook that is individualized to their medical circumstances in order to prepare for the possible outcomes of treatment. Research into how to support adults receiving immunotherapy and their caregivers has not kept pace with the adoption of these drugs as standard of care. Development of effective

strategies for communicating the risks and benefits of immunotherapy to patients and their caregivers is therefore a critical need in this rapidly evolving clinical landscape.[9]

Videos and question prompt lists improve patient medical understanding and communication skills. Several evidence-based strategies exist to improve patient and caregiver understanding of complex medical topics, including educational videos and question prompt lists. Documentary-style videos about possible health outcomes improve knowledge and reduce patient uncertainty about complex medical situations.[10,11,47] Video interventions ensure consistency in the delivery of the educational message, and may be a more accessible information source for patients with low health literacy.[48] Yet, patients and caregivers prefer to receive medical information from their trusted physician who can personalize health information.[49] One way to augment patient-clinician communication and guide conversations toward particular topics is by providing patients with a list of suggested questions that patients can choose to raise with their oncology team. Question prompt lists (QPL) empower patients with cancer to ask more questions and help them articulate the topics about which they feel uncertain, resulting in improved knowledge and decreased anxiety.[12,13,50]

2.2 Our research team at MGH has conducted two studies to explore the experiences of patients with metastatic cancer and their caregivers communicating with their oncology team about novel cancer treatments, including immunotherapy and targeted therapies (18-356 and 18-562). In our study of communication about immunotherapy (18-562) we have audio-recorded oncology visits and conducted interviews with patients and their caregivers to gain insight into unmet information needs related to immunotherapy via qualitative analysis. Our qualitative data indicate that patients and caregivers have high expectations of benefits from immunotherapy, and limited understanding about its risks. One patient with metastatic melanoma stated: "When I first found out I had melanoma, I thought it was a death sentence. But I was very excited to find out that there were actually options and the potential for a cure. Patients in our study also demonstrated a need for additional support in absorbing the information they receive. For example, another patient described, "Whenever I go to the doctor I just sort of blank out half the time. I'm still in a state of shock with the whole thing somewhat. Sometimes I'm there physically but I'm not there mentally, I guess."

We are also surveying 100 patients who have recently initiated immunotherapy for metastatic melanoma or NSCLC to evaluate their knowledge of the risks, benefits, and goals of immunotherapy (18-562). Our preliminary data demonstrates that patients are uncertain about many aspects of immunotherapy, including the likelihood of response to treatment, the mechanism of action of immune checkpoint inhibitors, and the timing and possible severity of ICI toxicity. Many also believe that immunotherapy will cure their metastatic cancer.

These studies have provided invaluable insight into important gaps in patients' and caregivers' knowledge about immunotherapy and opportunities to improve communication with their oncology team. We will address this lack of understanding in the educational video and QPL that we will refine and pilot test in this study. Study patients and caregivers have also helped us to refine our methods for screening and recruitment as well as data collection in the MGH Cancer Center, which will be useful in the proposed study.

2.3. This intervention will be the first evidence-based, rigorously developed tool to support patients' and caregivers' understanding of a new treatment modality that is now widely used in

oncology. Our intervention incorporates patients' and caregivers' perspectives, which is essential to ensure any supportive care intervention is appropriate, acceptable, and patient-centered.[51,52]. A small number of educational videos about immunotherapy have been created by pharmaceutical companies and oncology professional societies, but none have been developed with input from the target population. These videos emphasize the anti-tumor effects of immunotherapy and make no mention of possible toxicities which likely exacerbates patients' and caregivers' misperceptions about this therapy.[51,54] Our ongoing mixed methods studies suggest that patients and caregivers misunderstand the goals and risks of immunotherapy, and we will address these common misunderstandings in our educational video and QPL. In addition, our intervention combines two evidence-based strategies to ensure that patients and their caregivers are not only better educated, but also engaged in more effective communication with their clinicians. A common criticism of educational interventions, such as videos, is that they are not integrated into clinical care and do not foster patient-clinician communication.[48] As it is not possible for a video to have tailored information about how a patient's health status or cancer-related factors may influence their particular outcomes, patients and caregivers need accompanying tools to help them translate the general information in the video into a personalized discussion with their oncology clinician. QPL are ideal for this objective. Yet, no QPL specific to treatment with immunotherapy has been developed to date.

3.0 Inclusion and Exclusion Criteria*

3.1 We are requesting a Waiver of HIPAA Authorization in order for our team to perform an initial screening process that requires review of the electronic medical record. This waiver is being requested to allow the research team to screen the oncology clinic schedules and identify potential study participants from a minimal chart review. In accordance with the DF/HCC policy: (1) this Waiver is being sought solely to review Protected Health Information as necessary to prepare a research protocol; (2) the Waiver will not include removing Protected Health Information from the Covered Entity by the researcher, and (3) the Protected Health Information for which we are requesting access is necessary for research purposes.

We will also attend weekly meetings of the thoracic oncology and melanoma oncology group in which new patients are discussed, in order to identify eligible patients and review their eligibility with the oncology teams.

3.2 We will recruit patients with inclusion and exclusion criteria as defined below:

Table 1. All participants (Patients and Caregivers)

Inclusion Criteria
1. Age 18 or older
2. Ability to read and respond in English
Exclusion criteria
1. Prior history of treatment with an immune checkpoint inhibitor
2. Major psychiatric condition or comorbid illness that prohibits participation in the study
3. Cognitive impairment that prohibits provision of informed consent or participation in the study

4. Pregnant women
5. Prisoners

Table 2. Patient Criteria (in addition to Table 1)

Inclusion Criteria
1. Receiving care in the MGH Cancer Center
2. Diagnosis of advanced cancer, including: advanced, incurable lung cancer, including stage IV non-small cell lung cancer (NSCLC), unresectable stage III NSCLC, extensive-stage small cell lung cancer, melanoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, basal cell carcinoma, breast cancer, colorectal cancer, gastric cancer, esophageal cancer, hepatocellular cancer, renal cell carcinoma, bladder cancer, head and neck squamous cell carcinoma, cervical cancer, endometrial cancer, and mesothelioma.
3. Plan to initiate immunotherapy with an ICI (e.g. pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab, avelumab, cemiplimab, or combination), per clinician documentation in the electronic health record or study staff communication with clinician

Table 3. Caregiver Criteria (in addition to Table 1)

Inclusion Criteria
1. Identified as "a supportive person involved in their cancer care" by a patient enrolled in the study.

Eligibility criteria (Tables 1-3) will maximize study generalizability and rigor and take into consideration the limitations of the population under study. We will include patients with advanced cancer who receive their care in the MGH Cancer Center, and their caregivers.

We will include adult patients and caregivers who are over 18. We will exclude patients who had prior history of treatment with an immune checkpoint inhibitor. We will also exclude patients who are not English-speaking because our video is only currently available in English. Additionally, we will exclude patients who are not cognitively able to consent to participate in the study or participate in study activities, as judged by the study team or their oncology team. We will exclude pregnant women and prisoners, though these groups are unlikely to be represented in our population.

In addition to patients with advanced cancer, we will also include the caregivers whom enrolled patients identify as involved in their cancer care.

3.3 We will not include adults who are unable to consent. We will not include persons under 18 years of age. We will not include prisoners. We will not include pregnant women.

4.0 Study-Wide Number of Subjects*

4.1 This is a single-site study. We will accrue a total of 221 participants: 10 patients and 5 caregivers in Part 1, and 138 patients and 68 caregivers in Part 2. Every patient included in the study will be invited to include a caregiver; in our experience, about 50% of patients have a

caregiver interested in participating, thus caregiver total is inexact and reflects an estimate of how many caregivers will enroll. Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC Policy REGIST-101.

5.0 Study-Wide Recruitment Methods*

N/A. This is a single-site study at MGH. Local recruitment methods are described later in the protocol (see section 22.0)

6.0 Multi-Site Research*

This study is a single-site study that will be conducted at MGH.

7.0 Study Timelines*

7.1 Individuals will remain in the study from their enrollment to the study close, since we will be conducting a medical record review as part of the analysis. We anticipate that we will enroll all subjects over the course of three years, by July 2023. We will complete the study and all associated analyses by 2024, four years after study initiation.

8.0 Study Endpoints*

8.1 After providing informed consent, patients and caregivers will complete study assessments upon enrollment in the study, within 72 hours of their first ICI infusion, and at six weeks of follow-up. The primary study endpoints/outcomes are feasibility of the intervention and immunotherapy knowledge at 72 hours, measured by a knowledge survey. The secondary endpoints/outcomes are anxiety and communication with the oncology team, measured by the number of questions participants ask at their oncology visit prior to first immunotherapy infusion.

8.2 This is a low-risk educational intervention and we do not anticipate a need for safety endpoints.

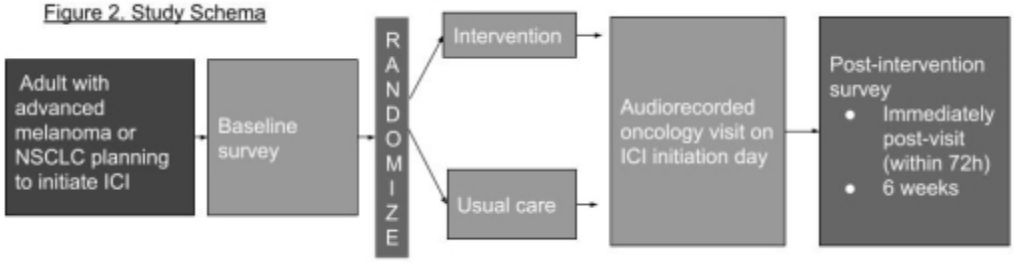
9.0 Procedures Involved*

9.1 In this two-part study, we will 1) refine and 2) pilot test an intervention to improve patient and caregiver knowledge and increase communication with their oncology team about immunotherapy. The intervention involves watching a video developed by the study team to educate patients regarding the risks, benefits, and potential outcomes of immunotherapy treatment and reviewing an immunotherapy-focused QPL prior to ICI initiation.

In Part 1 of this study, we will conduct a small open pilot (n=10) to refine the intervention and study procedures.

In Part 2, we will conduct a single-site pilot randomized controlled trial including 130 patients and their caregivers, to evaluate the feasibility of intervention delivery, and the preliminary efficacy of the intervention in improving patient and caregiver knowledge (primary outcome), enhancing patient-clinician communication, and reducing anxiety (secondary outcomes). We will assess these endpoints prior to the intervention (or usual care) and within 72 hours of the oncology visit and ICI infusion and at 6 weeks (±1 week) after the visit.

Figure 2. Study Schema



9.2 We will use the following study procedures, described below.

Background

Given the lack of evidence-based interventions to prepare patients and caregivers for the possible outcomes of immunotherapy, we have developed an intervention that combines watching an educational video and reviewing a question prompt list (QPL) prior to an oncology visit, for patients with advanced cancer initiating immunotherapy and their caregivers. We have developed an educational video about immunotherapy based on our prior research and clinical experience. We utilized an established, successful strategy to develop the video by first scripting a verbal narrative with input from patients, caregivers, oncologists, and palliative care physicians, and then creating visual images to accompany the narrative that help patients and caregivers understand the possible outcomes of immunotherapy for advanced cancer. The narrative incorporates guidance from expert oncologists on the most up-to-date data about risks and benefits of immunotherapy. To accompany the video, we have developed a preliminary QPL, using data from our mixed methods and survey studies, expert clinician input, and prior examples of cancer treatment-focused QPLs from the literature.[12,13]

Part 1 (Open pilot study to refine the intervention):

Patients will be screened and recruited as described in sections 3.1 and 22. After providing informed consent to participate in the study, the Clinical Research Coordinator (CRC) will request patients' and caregivers' email address (or preferred method of being contacted) in order to send them a brief baseline survey, a link to an educational video, a PDF alternative to the video, and a question-prompt list (QPL). The CRC will ask the patient (and caregiver, if applicable) to watch the video and review the QPL prior to their oncology visit and also re-contact participants via phone and/or email 24 hours before their oncology visit to remind them. When the participant(s) presents for the oncology visit, the CRC will again remind patients to review the video and QPL while they wait for their oncology visit. Prior to study initiation, we will obtain consent to record each clinician in our clinic who sees potentially eligible patients. This consent will be requested via email (Appendix 30.3) which will include the informed consent document. Before the oncology appointment, the CRC will place a digital audio-recorder in the exam room. After the visit, the research coordinator will retrieve the recorder and remind participants of the remaining study procedures. These include a short survey about their knowledge of immunotherapy, anxiety, and comfort with the intervention as well as a brief exit interview about their experience viewing the video and using the QPL. Specifically, in the exit interview, participants will be asked about the applicability, clinical relevance, length and timing of the

intervention, as well as any challenges patients and caregivers experienced and whether they were satisfied with the intervention.

Part 2 (Randomized trial of intervention):
Patients will be screened and recruited as described in sections 3.1 and 22. After providing informed consent to participate in the study, patients (and their caregivers if applicable) will be randomized as a dyad to the intervention or usual care arm (control group). Randomization will be carried out using the permuted block approach with stratification by cancer type, and patient-caregiver dyads will be assigned to the same study arm. Upon enrollment, patients or patient-caregiver dyads in both arms will receive the baseline survey (electronically or over the phone). Participants in the intervention arm will subsequently be directed to the video and QPL upon survey completion. A PDF alternative to the video will be sent to those unable to view the video. We will re-contact patients or dyads on the intervention arm via phone and/or email 24 hours before their oncology visit to remind them to watch the video and review the QPL. Participants on the usual care arm will have the option to receive the video and QPL after their study participation concludes. The CRC will meet participants in both arms at their subsequent appointment to to place a digital audio recorder in the exam room. Both the patient and oncologist will be recorded and the recordings will be transcribed to include the patient and oncologist participation in the conversation. For participants in the intervention arm, a final reminder will be given by study staff to review the video and QPL. Following this appointment, the CRC will collect the audio-recorder and participants in both arms will be asked to complete a follow-up survey within the next 72 hours. We will again administer this survey 6 weeks (±1 week) after the intervention.

9.3 The greatest risk of study participation is loss of confidentiality. We outline ways that we will mitigate this risk in section 24.

The sources that will be used to collect data from participants are included as attachments to this protocol submission.

Baseline Survey (attached)

Follow-up Survey 72 hours (attached)

Follow-up Survey 72 hours Usual Care (attached)

Follow-up Survey 6 weeks (attached)

Follow-up Survey 6 weeks Usual Care (attached)

Appendix 30.1: Exit Interview Guide

Appendix 30.2: Question Prompt List

9.4 Details about the data to be collected from participants and the electronic health record (Epic) are listed below.

Data to be collected	Source	Baseline	72 hours	6 weeks
Demographic data: age, gender, race, income	Survey	x		
Health literacy: confidence in filling out medical forms[64,65]	Survey	x		
Immunotherapy knowledge assessment (Appendix 1)	Survey	x	x	x
Prognostic awareness: two items about the goal of cancer treatment[65,66]	Survey	x	x	x
Anxiety: State and Trait Anxiety Inventory[66,67]	Survey	x	x	x
Optimism: 10-item Life Orientation Test	Survey	x		
Participant satisfaction and comfort with the intervention (intervention only): 1) Participants' comfort with the intervention, 2) Whether they found the intervention helpful 3) Whether they would recommend it to others[10]	Survey		x	
Clinical variables: date of diagnosis and cancer details (e.g., stage, treatment details including drug name and dates, toxicity or progression after immunotherapy)	Epic			

10.0 Data and Specimen Banking*

Data collected directly from participants and data extracted from the medical record will be stored in study databases on encrypted, password-protected Partners servers. The data will be stored for the duration of the study. Access to data will be limited to the principal investigator and co-investigators and research assistant, who will all be up to date in research confidentiality training.

11.0 Data Management* and Confidentiality

11.1 Data analysis plan.

Part 1: Analyses for Aim 1 will be descriptive and qualitative in nature to gain input from participants in the open pilot of 10 patients and their caregivers to identify themes of their experiences with the intervention. Caregiver analyses will be exploratory, and all analyses will analyze patients and caregivers separately. We will use descriptive statistics to tabulate the proportion of patients and caregivers who complete study activities and a framework approach to analysis of exit interview transcripts, including coding transcripts in qualitative software, and synthesizing codes into themes to identify opportunities for improvement. We will present the themes from participant feedback to the scientific advisory committee and key stakeholders and propose refinements to the intervention, and then refine it according to their input.

Part 2: Feasibility and acceptability: We will determine the proportion of patients who enroll in the study among all eligible patients, which includes all patients who both are identified on our

chart review screen. We will monitor and confirm participant use of the intervention by electronically tracking completion of viewing the video and asking patients about their use of the QPL.

Feasibility of the trial will be demonstrated if at least 70% of approached participants are enrolled and if at least 80% of participants randomized to the intervention watch the video and review the QPL. Estimates of enrollment rate and intervention completion rate from this pilot trial will inform the design of a future large-scale randomized trial. If 185 eligible patients are identified and approached, of whom 130 are enrolled (70% enrollment), the exact 95% confidence interval (CI) for enrollment rate will be (62.8%, 76.5%). If 52 of 65 intervention participants complete the intervention (80% completion) the exact 95% CI for completion rate will be (68.2%, 88.9%).

Preliminary efficacy: The primary outcome is participant knowledge, as measured by the immunotherapy knowledge assessment. The secondary outcomes include participant anxiety, and communication with the oncology team, measured by the number of questions asked during the oncology visit.

Analyses of all endpoints in the RCT will be conducted according to the principal of intention-to-treat and will utilize a 2-sided significance level of 0.05. Means and 95% CI for patients' knowledge scores (primary outcome) and anxiety (the state subscale of the State and Trait Anxiety Inventory; secondary outcome) will be computed by arm for the baseline, 72-hour and 6-week timepoints, and effect sizes (Cohen's d) for change from baseline to 72 hours and from baseline to 6 weeks will be calculated. We will use analysis of covariance (ANCOVA) model to adjust for baseline scores and covariates such as age and health literacy. Mixed effects linear regression models will be used to evaluate the effect of the intervention on outcomes across both post-intervention timepoints while adjusting for baseline values and other important covariates. Interaction terms will be used to evaluate whether the effect of the intervention on a given outcome is consistent or varying across the 72-hour and 6-week assessments. The number of questions asked by patients and caregivers (secondary outcome) will be assessed by coding the transcripts of audio-recorded oncology visits and compared between arms using the negative binomial model.[12] Exploratory analyses will include using ANCOVA to analyze change in prognostic awareness and optimism from baseline to 72 hours in both patients and caregivers and exploring possible moderators of the effect of the intervention such as age or health literacy using linear mixed models.

11.2 Power analysis. The primary outcome of this trial is feasibility. We provide a power calculation for the secondary, preliminary efficacy outcome in order to indicate the effect size that could be observed in this study. With 65 patients per arm, we will have 80% power to detect an effect size of 0.5 (Cohen's d) for change from baseline to 72-hour knowledge scores at a two-sided, significance level of 0.05. We anticipate that we will enroll ~65 total caregivers in both arms based on prior studies; the purpose of the caregiver analyses is exploratory. We will consider the effect size of the intervention in this pilot trial when designing an adequately powered efficacy RCT, though acknowledge that pilot effect sizes may over- or under-estimate the true effect.[64]

11.3 We will ensure the security of the data by limiting data access to study team members who have completed CITI training and who are authorized as study team members by inclusion in this IRB application or a subsequent amendment. Data will be stored in a password- protected, encrypted Redcap database and Dropbox accounts on a secure server. We will assign participants a study ID and maintain one file linking the IDs to patient identifiers such as name and medical record number, and in all other files, participant information will be linked only to non-PHI study IDs. Audio files (of oncology visits and interviews) will be shared with the HIPAA-compliant company Transcribeme.com for transcription services. Transcribeme.com is "fully compliant with Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements for Medical Transcriptionists, with multiple safeguards designed to protect the privacy and security of personal health information." The ways in which Transcribeme keeps transcriptions confidential is detailed here: https://transcribeme.com/hipaa-compliance/

During analysis of data, names and other PHI will be removed from the transcriptions and they will be tagged by study ID and date of visit/interview only. Audio files and data will be kept in secure databases for the study duration, and then hard copies of consent forms and surveys will be placed in long term storage or destroyed. Audio records will be destroyed once the study ends (enrollment and data analyses).

11.4 We will build quality control into the database and survey instruments we use to collect data. For example, when patients complete a survey that has been assigned to them, they will need to enter their initials as confirmation they have been assigned a link that corresponds to their record in the database. We will use logic in the questions to prohibit responses that do not correspond to appropriate date ranges, and will provide drop down options when possible. The research assistant will double enter all chart review data.

11.5. There will be no specimens collected. See Section 9.4 for details about data to be collected. We will assign participants a study ID and maintain one file linking the IDs to patient identifiers such as name and medical record number, and in all other files, participant information will be linked only to non-PHI study IDs. Data will be kept in a password-protected, encrypted database on a secure Partners server. Data will be stored for the study duration and thereafter archived as de-identified files.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

This study does not involve more than minimal risk to subjects. Nevertheless, we have developed the following Data and Safety Monitoring Plan:

Data and Safety Monitoring Plan

The purpose of the data and safety monitoring plan is to establish standards that will ensure that this protocol complies with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements, and applicable DF/HCC Standard Operating Procedures.

General Approach: We have developed a comprehensive data and safety monitoring plan for the project. Research team meetings will take place weekly, including review of study protocol, assessment procedures, and issues related to recruitment, data collection, and management.

Study staff will discuss any human subject issues that arise.

General Roles and Responsibilities: We will use several coordinated strategies to monitor study recruitment, enrollment, and retention. We will closely track collection of patient-reported assessments and completion of study sessions. We will document and track all study decisions made and actions taken and review them at the weekly team meetings.

Informed Consent Requirements. The DF/HCC approved informed consent document will serve as a template for the informed consent.

Protocol Confidentiality. Breach of confidentiality is a concern in all studies with human subjects. Safeguards will be put in place to ensure that participant information is kept private and confidential. Digital audio recordings will be erased within one year after study completion. All data will be stored in locked cabinets located in the PI's office as well as password-protected files, accessible only to trained study staff. All study staff are trained in human subjects research methods and protection of participant confidentiality. Participant data will be identified by an ID number only, and a link between names and ID numbers will be kept in a separate file under lock and key. Information about participants will be retained during the course of the study and one-year after study completion.

Data Management Organizational Structure Data. The study team will routinely evaluate the data and discuss any problems and questions at regular weekly team meetings. All study data (including data from the Electronic Health Record) will be stored on password protected files.

Data Safety and Monitoring Plan. The following procedures will be followed to ensure the safety of study participants and the validity and integrity of data:

- Data Repository: The MGH Cancer Outcomes Research and Education Program (CORE) has established procedures and technologies for data collection and management. The PI will oversee all aspects of data collection and management for the study. We will be responsible for generating reports and datasets for quality control and data analysis. Data management activities will utilize both LabArchives and REDCap, a HIPAA-secure, web-based survey application for electronic collection and management of research and clinical trial data. Data management reports will be generated and discussed during weekly study team meetings.

- Serious Adverse Events: Expedited review will occur for all serious adverse events and notification shall be made to the DF/HCC IRB.

- Non-Serious Adverse Events: At weekly meetings, the research team will discuss summaries of the numbers and rates of adverse events by treatment group. Reports will include type and severity of events.

- Other Safety-Related Reports: At weekly meetings, the research team will review treatment retention and reasons for dropout or withdrawal by treatment group.

- Study Stopping Rules: We do not have a pre-specified stopping rule given the low-risk

nature of the study. If at any point the DF/HCC or study investigators judge that the risks of study procedures outweigh the benefits, the project will be stopped immediately.

- Procedures to ensure confidentiality, preparation of reports, minutes, and recommendations: We will prepare study reports and circulate them during weekly meetings. At the conclusion of each meeting, the PI will determine whether any changes in the conduct of the trial are recommended.

13.0 Withdrawal of Subjects*

Participants will be withdrawn from research only if their clinical condition changes such that they are no longer able to participate in any study procedures prior to data collection. Participants who only complete part of the study will have their data included in analysis. Participants may voluntarily withdraw from the study at any point, in which case a report will be made of their reason for withdrawal and submitted to the IRB. Participants who choose not to contribute further information in a survey, semi-structured interview, or other procedures will be asked if they are willing to allow the data they have provided up until this point to be included in analysis. If they choose to withdraw completely, their data will be removed from the study database.

14.0 Risks to Subjects*

14.1 As this is a study to refine and pilot test an educational intervention, participants will not be at any risk for physical harm because of study participation. Participants may find some of the questions or information areas covered in the surveys, educational video, or question prompt list to be emotionally upsetting because these materials refer to their cancer, and if so, participants may experience some distress. We will provide participants with an overview of what the interviews will entail and emphasize the voluntary nature of participation, and give participants ample opportunity to withdraw from the study if they feel uncomfortable.

The main risks to participants will be loss of confidentiality. This risk is unlikely, as we will take every precaution, including collecting the minimum necessary dataset to conduct the research, de-identification of the dataset, and storage on password-protected, encrypted devices. We will keep a log that connects patient records to identifiers in order to facilitate chart review and to allow for re-contact of subjects if necessary, but we will otherwise minimize the individually identifiable private information collected, and will inform the participant of the kind of information that will be collected of informed consent. Access to individually identifiable information about human subjects will be limited to the principal investigator and the research assistant. We will de-identify the dataset prior to sharing data with other members of the research team. The records and data will be kept in a password-protected, encrypted database on a secure MGH server.

14.2 There are no procedures that patients will undergo during participation in this study that could have unforeseeable risks.

14.3 Pregnant women will not be included in this study.

14.4 There are no risks to others who are not participants in this study.

15.0 Potential Benefits to Subjects*

15.1 Potential benefits to patients are improved knowledge about immunotherapy and increased communication with the oncology team (the hypotheses under investigation). We will quantify knowledge at 72 hours and 6 weeks post-intervention, though the benefit of improved knowledge may endure beyond this timeframe.

15.2 There are no direct benefits to participants.

16.0 Vulnerable Populations*

The research will not involve persons from groups vulnerable to coercion or undue influence. We will not include pregnant women, prisoners, children, or cognitively impaired adults.

17.0 Community-Based Participatory Research*

This study is part of a broader research effort to improve supportive care interventions for patients with advanced cancer who receive immune checkpoint therapy treatment. Thus, we are seeking the participation and input of members of the community as represented in the MGH population to refine our intervention to improve health outcomes. We aim to include representation of patient and caregiver perspectives from diverse socioeconomic backgrounds, to the degree permitted by our study sample.

18.0 Sharing of Results with Subjects*

In this trial of an educational intervention, there are no diagnostic results or outcomes that will have clinical relevance to patients or their treating physicians. As a result of participating in this intervention, patients and caregivers may gain greater awareness of their treatment regimen and the potential outcomes of treatment, but we do not know that for certain.

19.0 Setting

The proposed study will be conducted in the MGH Cancer Center. Participants will be recruited from MGH Oncology clinics, identified by chart review and at weekly clinics meetings. Patients' and caregivers' consent will be obtained remotely via telephone, and participants will complete the initial survey, video or PDF alternative, and question prompt list remotely via

the internet or over the phone. Patients who do not have the ability to watch the video on their own will have the option of viewing it in person before their appointment, either in the waiting room with headphones or in their appointment room. The recording of the appointment will take place at Massachusetts General Hospital, and follow up interviews (for Part 1) will take place by phone. Follow-up surveys will take place in person during the patient's infusion or remotely (electronically or over the phone).

There will not be a community advisory board for this study. There will not be any research conducted outside of MGH.

20.0 Resources Available

20.1 Study team qualifications:

Laura Petrillo, MD (Principal Investigator): Dr. Petrillo is an Instructor of Medicine at Harvard Medical School. She is a palliative care physician in the MGH Outpatient Palliative Care Clinic. Dr. Petrillo will be responsible for all aspects of this study, with mentorship and guidance from Drs. Temel and Greer. Specifically, Dr. Petrillo will enroll participants and collect data with the help of the research assistant, analyze the data and synthesize findings into a manuscript for dissemination. Dr. Petrillo has extensive clinical research experience and advanced training in epidemiology, biostatistics and clinical research methods. She has all of the skills necessary to perform the proposed project. She is the current PI of two DFCI/HCC IRB-approved studies, 18-356 and 18-562.

Jennifer Temel, MD (Study Advisor) Dr. Temel is a Professor of Medicine at Harvard Medical School and the Director of the Cancer Outcomes Research and Education (CORE) Program at the MGH Cancer Center. She is a medical oncologist who specializes in lung and esophageal cancer and serves as the Clinical Director of Thoracic Oncology at the MGH Cancer Center. She is an accomplished health services researcher whose research focuses on studying novel health services delivery models, developing interventions to improve patients' symptom burden, quality of life and care, and enhancing communication between patients and clinicians. She has successfully completed numerous studies evaluating supportive care interventions in patients with cancer. As Director of CORE, she oversees research focusing on palliative and end-of-life care, psychiatric oncology, symptom management, novel health service delivery models, and survivorship. Dr. Temel is Dr. Petrillo's primary research co-mentor with Dr. Greer. She and Dr. Greer meet weekly with Dr. Petrillo to help with study oversight and data management.

Joseph Greer, PhD (Study Advisor) Dr. Greer is an Associate Professor of Psychology at Harvard Medical School. He is clinical health psychologist and the Program Director of the Center for Psychiatric Oncology & Behavioral Sciences at MGH. Together with Dr. Temel, Dr. Greer has enrolled >1000 patients on supportive care clinical trials.[57,60]. He is the Co-Director of the CORE Program at MGH, which conducts innovative research to improve oncology care for patients, families, and caregivers. Dr. Greer is Dr. Petrillo's primary research co-mentor with Dr. Temel. He and Dr. Temel meets weekly with Dr. Petrillo to help with study oversight and data management.

Clinical Research Coordinator - The research coordinator in the Cancer Outcomes Research and Education Program at MGH recruits patients, collects and manages data for clinical research studies, and oversees IRB communication as the study contact for this study and other research projects. The CRC meets at least twice a week with Dr. Petrillo for guidance on study management.

20.2 We will include a total of 130 patients with a recent diagnosis of advanced cancer and their caregivers. We estimate that 20-25 patients per month initiate ICI for advanced cancer at MGH, which will provide a sufficient pool from which to recruit our study cohort on the proposed timeline.

Dedication of time. Dr. Petrillo will devote 25% of her time to this research study. The study advisors, Drs. Temel and Greer, have protected time for mentorship through grant funding, and are committed to meeting with Dr. Petrillo once a week. The research assistant (Ms. Hsu) will dedicate 75% effort to this project.

Facilities. Dr. Petrillo has office space in the 3 Hawthorne building of MGH, including a workstation with a desktop computer and printer. Ms. Hsu has office space in the 1 Hawthorne building of MGH, including a workstation with a desktop computer and printer. Research procedures will be conducted in the MGH Cancer Center in Yawkey, in clinical rooms where thoracic oncology patients are seen. Additionally, procedures will take place remotely as surveys and other materials will be administered either over the phone or electronically.

Medical or psychological resources. Given that all patients will be clinical patients of the MGH Cancer Center, they will each have team that consists of a medical oncologist and the practice's nurse practitioner, registered nurses, and social workers. They will also have access to psychology resources as necessary. Should unanticipated psychological distress arise in the course of study data collection as described in Section 17.0, study staff will alert the Principal Investigator, who will contact the appropriate members of the patient's clinical team.

Training. All persons assisting with the research will have completed CITI training, and will be required to read the protocol and all study materials prior to engaging in study activities. Research assistant(s) will practice mock recruitment tasks such as informed consent and data collection procedures with the Principal Investigator prior to any participant contact, and will have the opportunity to shadow seasoned research assistants in the CORE program.

21.0 Prior Approvals

This research will be funded by Dr. Petrillo's Conquer Cancer Career Development Award from the American Society of Clinical Oncology. There are no other approvals necessary for this research.

22.0 Recruitment Methods

22.1 The research assistant will review the medical record to identify new patients in the oncology clinics. The research assistant will review the medical record to identify patients in the oncology clinics who plan to initiate immunotherapy, based on oncology progress notes that document this plan or a scheduled appointment in the MGH Infusion Center. We will send an opt-out email to the oncologist of eligible patients notifying the oncologist that a research assistant will call the patient. The research assistant will contact eligible patients electronically and by phone to introduce the study and obtain patients' informed consent. They will also ask if the patient has a caregiver who would be interested in participating in the study. All oncologists have given their approval for their patients to be approached about this study without an individual email to gain their approval for each patient, given its low-risk nature.

The oncologists will provide consent via email prior to initiation of the study. Study staff will email the elements of informed consent to oncologists who can provide consent over email.

22.2 The source of all patients will be current patients receiving treatment for advanced cancer in the MGH Cancer Center.

22.3 Methods included for our screening process include a) reviewing both previous and upcoming weeks in EPIC, attending weekly thoracic and melanoma meetings in which patients are reviewed, and communicating with clinicians. There will be no direct-to-patient advertising of this study.

22.4 Patients and caregivers will be recruited through a phone call from the research assistant. We include the script that the research assistant will use when they call patients to introduce the study as an attachment. If the patient (and caregiver, if applicable) approve of participation in the study, their verbal consent will be obtained over the phone. Additionally, their contact information will be obtained in order to provide them with the survey and other study materials. Oncologists will provide consent over email.

22.5 Participants will be paid $20 following completion of study procedures.

23.0 Local Number of Subjects

23.1 We will accrue a total of 210 participants: 10 patients and 5 caregivers in Part 1, and 130 patients and 65 caregivers in Part 2.

23.2 We anticipate that we will screen approximately 480 patients in order to identify 185 eligible patients, and anticipate that of those, 130 patients will provide consent (70%). We further anticipate that 104 (80%) will complete the study activities.

24.0 Provisions to Protect the Privacy Interests of Subjects

24.1 We will take every precaution to protect subjects' privacy interests, including collecting the minimum necessary dataset to conduct the research, de-identifying the dataset, and storing it

on password-protected, encrypted devices. We will keep a log that connects patient records to identifiers in order to facilitate chart review and to allow for re-contact of subjects if necessary, but we will otherwise minimize the individually identifiable private information collected, and will inform the participant of the kind of information that will be collected of informed consent. Access to individually identifiable information about human subjects will be limited to the Principal Investigator and the research assistant. We will de-identify the dataset prior to sharing data with other members of the research team. The records and data will be kept in a password-protected, encrypted database on a secure MGH server.

24.2 To make participants feel at ease, we will describe all study procedures, the information that will be collected from them and their medical record, and let them know how the information will be used and kept secure. There will be no examinations or procedures in this study.

24.3 We request a HIPAA Waiver as detailed in Section 3.1 so that the research team may screen the medical record to identify eligible patients. Patients who consent to participate in the study will be informed which aspects of their medical record will be accessed if they consent to participate, and they will also be asked to provide additional data in surveys. We will obtain HIPAA Authorization from participants during the in-person aspect of the research.

25.0 Compensation for Research-Related Injury

25.1 This research does not involve more than minimal risk to subjects.

25.2 Not applicable.

26.0 Economic Burden to Subjects

26.1 There will be no additional costs for which participants will be responsible, since we will not ask patients to present for additional visits for this study and the study activities will take a minimal amount of time that can be completed on a flexible schedule.

27.0 Consent Process

27.1 We will obtain patients' verbal consent via telephone, in accordance with the CON-100 SOP. The research assistant will contact patients who have a plan to receive immune checkpoint inhibitors for advanced cancer prior to their first infusion to introduce the study and obtain their verbal consent. Patients will be contacted via telephone and via a Patient Gateway (a secure communication platform within the electronic medical record which has a message option for "Research Recruitment"), if they have activated their Patient Gateway account (scripts attached for both). A copy of the verbal consent form and a patient fact sheet (attached) will be included in this Patient Gateway message. There will be no waiting period between the introduction of the study and patient enrollment. We will obtain HIPAA Authorization during the in-person aspect of the research. We will obtain clinicians' consent via email. We will email the elements of informed consent to the clinicians who can respond with their consent over email.

We are requesting to waive the written documentation of participants' informed consent and in its place, secure their verbal consent to participate in this research study. This waiver would grant us the ability to accept verbal consent in lieu of the traditionally signed consent form. Our research presents no more than minimal risk of harm to subjects, and does not involve procedures where written documentation of consent would normally be required outside of the research context. Participants will be reminded during the data collection process that their participation is voluntary, and that they have the right to withdraw from the study at any time.

Subjects will also receive an unsigned copy of the informed consent document detailing the information about the use and disclosure of their PHI. Study staff will ask participants their preferred method for receiving this document, electronically or by mail. Participants who prefer an electronic version will be sent the consent form through a secure, Partners-operated file-sharing platform (transfer.partners.org) or by secure email.

We will not include patients who do not speak English since we do not have access to the video under study in other languages. We will also exclude patients with cognitive impairment or other condition that would affect their ability to provide informed consent or participate in study activities. We will also exclude children since this study will take place in the adult oncology clinics at MGH.

28.0 Process to Document Consent in Writing

We are requesting to waive the documentation of consent given both the feasibility and the minimal risk of harm to subjects our study presents. Instead, participants will be consented verbally and receive a copy of this consent form after providing their verbal consent. We will be following the CON-100 SOP. This research does not present more than minimal risk to subjects. Consent documents are attached.

29.0 Drugs or Devices

N/A; this research does not involve drugs or a device.

30.0 Appendices

30.1: Exit Interview Guide

30.2: Question Prompt List

30.3: Clinician Consent to Audiorecord Email Template

30.1: Exit Interview Guide

Exit Interview Guide

Please rate the following on a scale of 1-4.
(1 = Quite dissatisfied, 2 = Mildly disappointed, 3 = Mostly satisfied, 4 = Very satisfied)

How satisfied are you with the amount of information included in the video? _____

How satisfied are you with the questions that were suggested in the question list? _____

How comfortable were you with using the list to ask your oncology team questions? _____

How satisfied were you with the virtual delivery of the video and question list? _____

How satisfied are you with the length of the study questionnaires you completed? _____

Please rate the following on a scale of 1-4.
(1 = Not at all likely, 2 = Somewhat likely, 3 = Likely, 4 = Very likely)

How likely are you to recommend this video and question list to another patient starting immunotherapy?

Please answer the following questions:

Is there anything else that you would have liked the video to cover?

Is there anything else that you would have liked the question list to cover?

Is there anything that you found helpful?

Is there anything that you found to be unhelpful?

30.2: Question Prompt List

What Can I Expect From My Cancer Treatment With Immunotherapy?

Most people with cancer have a lot of questions about what will happen next, but it can be hard to remember your questions during a medical visit. This is a list of questions about treatment with immunotherapy that other patients have asked their medical team. You might want to circle certain questions, or write in your own questions. You may share this list with your family or friends.

This question list accompanies a video entitled, "Immunotherapy and Immune Checkpoint Inhibitors," and is broken down into sections that go with the video. You may find that some questions feel right for right now, and some may be better to think about later. We suggest that you read the section header first.

Your medical team wants to know what is on your mind, and they are happy to answer all of your questions so that you feel ready and know what to expect. Please bring this list to your next appointment at the Cancer Center to go over with your medical team.

Section 1: What is immunotherapy?

Your oncology team will create an immunotherapy treatment plan that is specific to you and the kind of cancer you have. You may want to ask about the details below to help you understand YOUR plan. Use the lines at the bottom of each section to add your questions.

- What are the names of the immunotherapy medications I will I be receiving for my cancer?
- How often will I receive them, and for how long?
- What is the goal of immunotherapy for my cancer?
- Is it possible to cure my cancer?
- *When* will we know if immunotherapy is helping my cancer?
- *How* will we know if immunotherapy is helping my cancer?

- Where can I find more information about my cancer and treatment?
- _____
- _____

Section 2: Side effects and risks of immunotherapy.

Understanding immunotherapy side effects is an important part of becoming prepared for treatment. These questions will help you and your caregivers know what to watch for as you start treatment.

- What side effects of immunotherapy am I most likely to experience, if any?
- Will I experience the side effects people often have from chemotherapy, like hair loss, nausea, or increased risk of infection?
- When are side effects of immunotherapy most likely to occur?
- What should I do if I experience side effects?
- How should I reach my oncology team if I have side effects and who is the point person?
- Is it safe to take my current medications while I am on immunotherapy?
- Is it safe to take over the counter medications while I am on immunotherapy?
- _____
- _____

Section 3: What to expect in the future?

Some people find that it is helpful to know the range of possible outcomes from treatment so that they can prepare for the future, while others find this information stressful. If you or your caregivers think this information would help, here are some questions to ask your medical team.

- How likely is it that immunotherapy will work for my cancer?
- Is it possible to give me a time frame about how long I can expect to live?
- How will immunotherapy affect the amount of time I can expect to live?
- What is the best-case scenario? What is the worst-case scenario?
- Do I need to modify my activity while on treatment?
- Will immunotherapy affect my ability to do my normal activities?
- _____
- _____

Section 4: Coping with uncertainty.

Living with cancer and going through treatment are challenges that everyone responds to differently. As you go through immunotherapy treatment, you or your caregivers may need more support. Here are questions to help identify the resources available to you.

- What can I do to deal with stress from living with cancer and going through treatment?
- Who can I talk to if I experience problems with stress or sadness in dealing with cancer?
- Are there any services to help my family and me cope with cancer?
- Are there any organizations that might be helpful to my family and me in going through cancer?
- _____
- _____

Section 5: Caregivers and other important people in your life.

Many people going through cancer treatment receive support from other people in their lives. Your caregivers, family members, and friends may also need information and support.

- What resources are available to help me communicate with the important people in my life (including children) about my cancer and cancer treatment?
- Are there any resources specifically to support my caregiver(s)?

30.3 Clinician Consent to Audiorecord Email Template

Dear [Clinician],

We are conducting a study (20-410) to educate patients with advanced cancer and their caregivers about immunotherapy and enhance communication between oncologists, patients, and caregivers. This study involves audio-recording patients' first visit with their provider. These visits will be transcribed, anonymized and evaluated to help us describe how patients and clinicians interact and communicate. Please find an informed consent document with further information about the research attached. Do you give your consent to be recorded in these visits with any patients who have consented to the study?

Thank you!

[Staff Name]