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WILMOT CANCER INSTITUTE

An inpatient advance care planning intervention for older patients with hematologic malignancies

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Background

1.1. Many hematologic malignancies are diseases of aging.

Many hematologic malignancies are diseases of aging.[1,2] For example, the median age at time of diagnosis for patients with acute myeloid leukemia (AML), non-Hodgkin lymphomas (NHL), and multiple myeloma (MM) are 68, 67, and 69 years, respectively.[1] Recently, there have been advances in treatment options for older adults with hematologic malignancies. For example, in the last decade, lower-intensity outpatient treatments with reduced treatment-related mortality rates and potentially similar efficacy to standard first-line intensive inpatient chemotherapy have become available to patients with AML.[4-6] Despite hematologic malignancies being more common in older populations and recent treatment advances, survival rates for older adults with hematologic malignancies remain poorer than their younger counterparts.[1] In older patients with AML, for example, the median overall survival rates range from 6-12 months. In addition, hospitalizations due to treatment- and disease- related adverse events are common.

1.2. Patients with hematologic malignancies receive more aggressive care at the end-of-life (EOL) compared to those with solid tumors.

Previous studies have established quality indicators to guide optimal care at the EOL.[8,9] These quality indicators include healthcare utilization [emergency department (ED) visits, hospitalizations, intensive care unit (ICU) admission, life-sustaining treatments (LSTs), chemotherapy administration, and receipt of transfusion] at EOL, completion of Medical or Physician Orders for Life Sustaining Treatment (MOLST/POLST) forms, utilization of palliative care and hospice services, and place of death. Compared to patients with solid tumors, patients with hematologic malignancies are more likely to visit the ED, be hospitalized, be admitted to ICU, and to receive LSTs, transfusions, and chemotherapy at the EOL.[3,10,11] They are also less likely to complete MOLST/POLST forms in a timely fashion, less likely to receive palliative care and hospice services, and more likely to die in the hospital.[3,10] Therefore, interventions are needed to improve EOL care in patients with hematologic malignancies.

1.3. Advance care planning (ACP) may improve EOL care for older patients with hematologic malignancies.

ACP is a process that supports adults in understanding and sharing their personal values, life goals, and preferences regarding medical care. These decisions can then be recorded in MOLST/POLST forms to guide surrogate decisions makers if the patient loses decision making capacity. Our preliminary data demonstrates that among adults with AML and myelodysplastic syndrome (MDS) seen at the Wilmot Cancer Institute (WCI) and its affiliated community centers, most MOLST forms were completed late in the disease course.[12] Compared to patients who completed MOLST $\leq$ 30 days prior to death or never completed MOLST, those who

completed MOLST >30 days prior to death were less likely receive inpatient care and more likely to utilize hospice at the EOL, indicating early MOLST completion is associated with better EOL care. Interventions to improve access to ACP and MOLST/POLST completion can therefore be expected to improve EOL care.

1.4. Evidence-based interventions can improve access to ACP but are not tailored to older adults with hematologic malignancies.

The Serious Illness Care Program (SICP) is an evidence-based intervention to enhance EOL conversations between physicians and patients with advanced cancer in the outpatient setting.[13] It consists of the Serious Illness Conversation Guide (SICG) as well as training and system-level support for physicians to conduct conversations about ACP. In a phase III randomized trial, compared to the control arm, more patients and physicians in the intervention arm had serious illness conversations (96% vs. 79%) and these conversations occurred 2.4 months earlier and were more comprehensive and patient centered. However, less than 10% had hematologic malignancies. Therefore, we have adapted the SICP for older patients with hematologic malignancies based on feedback from clinicians [oncologists, palliative care physicians, advanced practice providers (APP), and nurses)], older patients with these diseases, and their caregivers.

1.5. Previous research has shown that advanced practice providers-initiated ACP discussions improve ACP engagement.

APPs play an important role in the care of patients, especially in the inpatient setting at the Wilmot Cancer Institute, alongside the attending physician and hematology/oncology trainee physician. APP-initiated ACP discussions have been shown to improve patient understanding of ACP and completion of advance directives for patients with cancer.[14] Furthermore, implementation of APP roles in inpatient settings, including critical care, have been shown to improve patient satisfaction and cost of care.[15] Therefore, an inpatient APP-delivered ACP intervention for patients with hematologic malignancies may improve care for this patient population.

1.6. Overall goal

The long-term goal of this proposal is to improve ACP access and EOL care in older patients with hematologic malignancies via an inpatient ACP intervention delivered by APPs and hematology/oncology trainee physicians (hereby referred to as fellows).

The objective of this two-year project is to create training materials and processes for an inpatient ACP intervention and to assess its preliminary efficacy in older patients with hematologic malignancies in a single arm study (comparing data to historical control).[13]

2.0. Aim and Hypothesis

2.1 Primary Aim

To adapt training materials and processes for an inpatient ACP intervention delivered by APPs and hematology/oncology fellows (completed).

2.2. Secondary Aim

To assess the feasibility of an inpatient ACP intervention, as well as the preliminary efficacy of the intervention on completion of advance directives (e.g., MOLST form, healthcare proxy form) and on EOL care (e.g., intensive care unit admissions, life-sustaining treatments, readmission rates, hospice enrollment, inpatient death).

2.3. Hypothesis

An inpatient ACP intervention delivered by APPs and hematology/oncology fellows will improve completion of advance directives and EOL care.

3.0. Study Design and Population

3.1. Study Setting

Wilmot Cancer Institute (WCI), University of Rochester Medical Center (URMC)

3.2. Study Type

Aim 1: Qualitative study (phase 1) - completed

Aim 2: Single-arm pilot study (phase 2)

3.3. Study Population

Aim 1 (completed): We will discuss the study at APP meetings and solicit interest in participation. Ms. Danielle Kindron will serve as the APP lead and has preliminarily solicited support from APPs on the inpatient hematology service. We will approach APPs in person or via email communications. We will conduct focus group interviews to obtain feedback on training materials (e.g., prerecorded vs. interactive sessions, duration of training) and processes (e.g., workflow, template to document ACP visit in the electronic medical record) in the inpatient setting. Interviews will be audio-recorded by study personnel and then transcribed. Two trained personnel ("coders") will extract and highlight themes from the transcripts. We anticipate up to 15 APPs will participate in this aim.

Results from Aim 1 will be used to adapt the inpatient APP-delivered ACP intervention for use in Aim 2 (these will be shared with APPs via email prior to Aim 2 so they can review how their feedback was used to adapt the intervention). In other words, Aim 2 will occur after Aim 1 has been completed.

Aim 2: We will conduct a single arm study of 50 older patients, their caregivers (up to 2 caregivers per patient), and APPs/hematology/oncology fellows. We will approach all APPs on the inpatient hematologic malignancy service for Aim 2, with a goal of between 10-15 APPs participating. We will discuss the study at hematology/oncology fellow meetings and PIs (Dr. Kah Poh Loh and Dr. Jason Mendler) will lead efforts to solicit support and involvement from fellows. We will approach all hematology/oncology fellows at Wilmot Cancer Institute for Aim 2, with a goal of between 10-12 fellows participating. We will consent up to 252 participants (75 patients, 150 caregivers, 15 APPs, 12 fellows) to account for screen fail or withdrawal with the target number being 50 patients and 100 caregivers.

3.4. Inclusion and Exclusion Criteria for Clinicians (Aim 1 and Aim 2)

Inclusion criteria:

Aim 1 (completed)

- APP on the inpatient malignant hematology service [including both physician assistants (PA) and nurse practitioners (NP)]

Aim 2

- APP on the inpatient malignant hematology service [including both physician assistants (PA) and nurse practitioners (NP)]
- Hematology/Oncology fellows at the Wilmot Cancer Institute

Exclusion criteria

- None

3.5 Inclusion and Exclusion Criteria for Patients (Aim 2)

Inclusion criteria:

- Age ≥60 years
- A diagnosis of hematologic malignancy [including but not limited to acute leukemia, myeloid malignancies (e.g., atypical CML, MDS/MPN overlap syndromes, CMML), multiple myeloma, lymphoma, or any other hematologic malignancies based on the primary oncologist's judgment]
- Able to provide informed consent
- Being managed in the inpatient setting
- English-speaking

Exclusion criteria

- None

3.6 Inclusion and Exclusion Criteria for Caregivers (Aim 2)

Inclusion criteria:

- Age ≥18 years
- Selected by patient when asked if there is a "*family member, partner, friend, or caregiver with whom you discuss or who can be helpful in health-related matters*"
- Able to provide informed consent
- English-speaking

Exclusion criteria

- None

3.7. Number of Subjects

Aim 1: We plan to enroll APPs on the inpatient malignant hematology service. This phase will consist of focus group interviews with APPs. We plan to enroll up to 15 APPs. We will conduct at least two and up to four focus groups. We anticipate thematic saturation will be reached with this number of participants based on previous studies (i.e., the point at which no new data emerge).[17,18]

Aim 2: We plan to enroll 50 patients total and their caregivers (up to 2 caregivers per patient if available) in 18 months. On average, 2-4 patients with hematologic malignancies are admitted to Wilmot Cancer Institute every day (and on average, the inpatient malignant hematology service cares for 15-25 patients daily). Our team has a proven track record in recruiting older patients with hematologic malignancies to supportive care and quality improvement studies (65-75% consent rate).[17,18] Therefore, recruiting 50 patients and their caregivers [approximately 150 participants (50 patients; 100 caregivers), but can consent up to 225 patients/caregivers to account for screen fail/withdrawal; 75 patients and 150 caregivers] over 18 months is feasible. Patients and caregivers participation in this study will last approximately 4 weeks.

APPs who consent to the study in Aim 1 will also be consented to participate in Aim 2. APPs can also consent and join the study in Aim 2, after Aim 1 has been completed. Therefore, participation in Aim 1 of this study will last for 1 day for APPs and participation in Aim 2 of the study will last approximately 18 months for APPs. We plan to consent hematology/oncology fellows to participate in this study for Aim 2 only, since Aim 1 of this study has already been completed. Therefore, fellows will not participate in the focus group interviews. Participation in this study will last approximately 18 months for hematology/oncology fellows participating in Aim 2.

3.8. Gender of Subjects

The gender ratio of enrolled patients will be similar to the gender ratio of each hematologic malignancy in older adults (e.g., approximately 1.2:1 to 1.5:1 male to female ratio for AML patients).[19,20]

3.9. Age of Subjects

We will recruit patients with hematologic malignancies aged 60 and above (from date of consent, confirmed on electronic medical record).

3.10. Racial and Ethnic Origin

In Rochester, New York, Whites, African Americans, and Hispanics make up approximately 65%, 30%, and 5% of the population (Race and Ethnicity in Rochester, NY statistical atlas). We expect participants to be similar to these statistics. Certain hematologic malignancies are more common in Caucasian individuals, including leukemia and lymphoma, while hematologic malignancies such as multiple myeloma are more common in African American individuals. We expect our participants will be similar to this epidemiology. As enrollment is limited to English-speaking patients, we predict a higher percentage of Caucasian individuals. The study does not restrict enrollment based on race or ethnicity. Because our intervention materials are written in English, we will only enroll English-speaking patients.

3.11. Vulnerable Subjects

Recruitment will exclude vulnerable populations such as fetuses, neonates, children, pregnant women, prisoners, and institutionalized individuals. We will also exclude adults who are deemed to not have decisional capacity and those who lost their consent capacity during the study period, as per their treating oncologist.

4.0. Recruitment and Consent

Subjects (APPs, hematology/oncology fellows, patients, and caregivers) will be enrolled at the URMC WCI.

To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subject Research will be followed.

4.1. Identification of Study Subjects, Recruitment, and Consent Procedures

We will discuss the study at APP/hematology/oncology fellow meetings and solicit interest in participation. Ms. Danielle Kindron will serve as the APP lead and has preliminarily solicited support from APPs on the inpatient hematology service. Dr. Kah Poh Loh and Dr. Jason Mendler will lead efforts to solicit support and participation from hematology/oncology fellows. We will approach APPs/hematology/oncology fellows in person or via email communications.

For clinicians, email communications will be used for the following purposes: to complete baseline and post-intervention surveys, notify clinicians of enrolled patients, schedule study visits, and schedule end-of-study interview. For patients and caregivers, email communications may be used for administering baseline and post-intervention surveys. Due to the setting of this study being inpatient, study coordinators will prioritize administering surveys and communications in person with patients and caregivers. In the event this is not possible, such as a patient is discharged or a caregiver is participating in the study remotely, then email communications will be used.

4.1.1 APPs/Hematology/Oncology Fellows

For in-person consent with APPs, study staff will contact APPs to formally consent to the study after the study has been discussed at staff meetings and/or the APP has been made aware of the study by Ms. Kindron. For in-person consent with hematology/oncology fellows, study staff will contact hematology/oncology fellows to formally consent to the study after the study has been discussed at hematology/oncology fellow meetings and/or they have been made aware of the study by Dr. Kah Poh Loh and/or Dr. Jason Mendler. Therefore, we will also discuss the study at staff/hematology/oncology fellow meetings and solicit interest in participation. Following the staff meeting, all APPs/hematology/oncology fellows who attended will be contacted via email. The study staff will offer to call or meet the APP/hematology/oncology fellow in person, if requested by the APP/hematology/oncology fellow, for consent. Otherwise, the APP/hematology/oncology fellow will consent via email through implied consent. We will obtain APP or hematology/oncology fellow email addresses from Ms. Kindron or Dr. Loh and Dr. Mendler, respectively. When appropriate, they will set up time to come meet the APP/hematology/oncology fellow to go over every detail of the study. If the APP/hematology/oncology fellow agrees, they will sign the consent with the study staff during this in-person encounter.

For implied consent with APPs/hematology/oncology fellows, study staff will contact APPs/hematology/oncology fellows via email. In the email, study staff will include a link to a

REDCap survey for APPs/hematology/oncology fellows. The survey will include the same information that can be found on the RSRB approved APP/hematology/oncology fellow information sheet. Therefore, when APPs/hematology/oncology fellows click the REDCap link, they will see the APP/hematology/oncology fellow information sheet. APPs/ hematology/oncology fellows will review the information sheet and click "I agree" at the end of the study if they would like to consent and enroll. If the APP/hematology/oncology fellow does not want to participate in the study, there will be an option for "I do not agree" at the bottom of the REDCap survey.

4.1.2 Patients

Patients will be identified by treating physicians, APPs, hematology/oncology fellows, and nurses of these physicians, and the study coordinators. The study coordinators will work closely with APPs/hematology/oncology fellows to identify patients who are admitted to the hospital with a hematologic malignancy (Aim 2). The study coordinator will contact the physician (or designee) and inform them of patient eligibility and ask permission to approach the patient. The principal investigator will address any eligibility questions that may arise.

For in-person consent with patients, below are the possible scenarios for obtaining consent.

1) Physician/APP/Hematology/Oncology Fellow/Study Investigator makes the initial contact and provides consent form, and patient signs consent on the same day: After confirming with the physician (or their designee) that a patient is a potential candidate for the study, the study staff will provide a consent form to the treating physician/APP/hematology/oncology fellow/study investigator so he/she can provide it to the patient during an in-person hospital admission. The physician/APP/hematology/oncology fellow/study investigator will go over every detail of the study during the hospital admission with patient. If the patient agrees, the patient will sign the consent form with the physician/APP/hematology/oncology fellow/study investigator during the same in-person visit. If the patient wants more information or wants to think about the study, the physician/study investigator (or their designee) will provide the patient with the "info only- do not sign" version of the consent document for the patient review.

2) Study staff makes the initial contact and provides consent form, and patient signs consent with the study staff on the same day: After confirming with the physician (or their designee) that a patient is a potential candidate for the study, the patient will be provided with an informed consent form by the study staff while admitted to the WCI. The study staff will introduce the study to the patients and go over every detail of the study. If the patient agrees, the patient will sign the consent form with the study staff during the same hospital admission with the study staff. If the patient wants more information or wants to think about the study, the physician/study investigator (or their designee) will provide the patient with the "info only- do not sign" version of the consent document for the

patient review.

4.1.3 Caregivers

For in-person consent with caregivers, patients will make the initial contact. After confirming with the patient that a caregiver is willing to speak with the study coordinator about the study, the study staff will approach the caregiver in-person in the hospital. The study coordinator will go over every detail of the study during the hospital admission with the caregiver. If the caregiver agrees, the caregiver will sign the consent with the study coordinator during the same in-person visit. If the caregiver wants more information or wants to think about the study, the study staff will provide the patient with the "info only- do not sign" version of the consent document for the patient review.

Consent for study procedures can be conducted remotely therefore in-person visits are not necessary if caregivers are not actively in the hospital with their respective patient. For verbal consent with caregivers, patient will make the initial contact. After confirming with the patient that a caregiver is willing to speak with the study coordinator about the study, the study staff then will call the caregiver via phone. The study coordinator will use the verbal consent script as a written aid and will go over every detail of the study with the caregiver to recruit them for the study. Study staff will sign and date it to confirm that he/she followed the script, and the caregiver agrees to participate in the study. An information sheet summarizing the study and caregiver's involvement will be provided/mailed/emailed to the caregiver for their records.

4.1.4 Informed Consent

Informed consent will be obtained from the patient by the study investigators or coordinators. Consent documents will be signed by the patient and maintained in the patient record with copies provided to the patient. Verbal consent documents with caregivers and APPs/hematology/oncology fellows will also be maintained in separate records with copies provided to caregivers and APPs/hematology/oncology fellows.

Waiver of documentation of consent:
We are requesting for waiver of documentation of consent as the research involves no more than minimal risk to the subjects (APPs/fellows via implied consent and caregiver via verbal consent) and involves procedures for which written consent is normally not required outside the research context. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality.

Alteration of HIPAA Authorization:
We are requesting an alteration of HIPAA authorization. We will provide an information sheet to caregivers who provided verbal consent and APPs/hematology/oncology fellows who provide implied consent. Verbal and implied consent will allow for reduction of in-person visits, thus

maximizing the safety of both participants and study staff. Nonetheless, when possible and if we are able to coordinate study and clinic visits, we will obtain written informed consent.

The study cannot be conducted without the use of protected health information (PHI) as we have to link patient reported data with medical history collected on electronic medical record. We have adequate plans to protect the PHI from improper use and disclosure. We will destroy identifiers after completion of the study for 7 years. We will not reuse or disclose the PHI to another person or entity other than the study investigators. The waiver will not adversely affect the privacy rights of the individual and the research cannot be practicably done without access to the use of the PHI.

4.1.5 Human Subject Protection

The University of Rochester Research Subject Review Board Investigator Guidance policy will be used to ensure that ethical standards for human subjects are upheld.

4.2 Participation

Regulations at the state, federal, and institutional level will be adhered to in regard to informed consent. Study participation is completely voluntary. After consenting, participants may withdraw from the study at any time for any reason, and they may do so without any repercussions. Participants may also be withdrawn by study personnel if it is determined that it is not favorable for the patient. All information regarding consent and withdrawal will be kept confidential.

4.3 Duration

Aim 1: The qualitative section of this study involves focus group interviews with APPs for 30-60 minutes. Participating APPs will be interviewed by the study team either in-person (in a private space) or via zoom. Interviews will be audio-recorded, uploaded to Box, and subsequently deleted from the audio-recorder.

Aim 2: At study initiation, APPs/hematology/oncology fellows will undergo a skill-based training session of the SICG (3 hours). APPs and hematology/oncology fellows will undergo the same skill-based training session. The SICG training session is a 2.5 to 3-hour training session that will be conducted via zoom or in-person and led by Dr. Thomas Carroll (palliative care physician). This training session will include standardized patient encounters for APPs/hematology/oncology fellows to practice using the SICG under the direct supervision of Dr. Carroll with real time feedback.

At baseline, study patients and consented caregivers will complete demographics and baseline measures. We will also collect demographic information from APPs/hematology/oncology fellows. We will perform a geriatric assessment that assesses the patient's overall health status

prior to ACP intervention. Following this, we will schedule an ACP visit with an APP/hematology/oncology fellow on the inpatient malignant hematology service during the same hospital admission. Their caregivers can join via in person, zoom, or phone (depending on COVID restrictions). During the ACP visit, the APP/hematology/oncology fellow will discuss ACP and EOL care and may facilitate completion of advance directives and a MOLST form if appropriate. This visit will be recorded. After the visit, they will complete post-intervention measures. Within 4 weeks of the ACP visit, we will conduct a semi-structured interview with the patient and caregiver (if available) either via video, phone, or in-person to elicit their experience with the visit and feedback on the ACP intervention. We will also conduct a semi-structured interview with APPs/hematology/oncology fellows who enrolled patients at the end of the study.

All audio-recordings will be uploaded to Box, transcribed by a professional transcription service, and subsequently deleted from the audio-recorder. After the study is completed, all participant data will be maintained for 7 years at URMC and will be kept in a password-protected database.

5.0. Registration

For Aim 1 (qualitative), registration information for APPs/hematology/oncology fellows will be collected and entered into REDCap.

For Aim 2, registration information for patients, caregivers, and APPs/hematology/oncology fellows will be collected and entered into the OnCore Database:

5.0. Registration Information for APPs/hematology/oncology fellows

- 5.0.1 Participant's identification
  - 5.0.1.a First and last names
  - 5.0.1.b Birth date (MM/DD/YEAR)
  - 5.0.1.c Gender
  - 5.0.1.d Race
  - 5.0.1.e Five-digit zip code
  - 5.0.1.f Ethnicity

5.1. Registration Information for Patients

- 5.1.1 Site
- 5.1.2 Most recent IRB approval date
- 5.1.3 Name of person registering study participant
- 5.1.4 Eligibility verification
- 5.1.5 Verification that consent form has been signed and date signed

5.1.6 Treatment facility (WCI)
5.1.7 Participant's identification
5.1.7.a First and last names
5.1.7.b Birth date (MM/DD/YEAR)
5.1.7.c Gender
5.1.7.d Race
5.1.7.e Medical Record Number
5.1.7.f Ethnicity
5.1.7.g Date of baseline visit

5.3. Registration Information for Caregivers

5.3.1 Participant's identification
5.3.1.a First and last names
5.3.1.b Birth date (MM/DD/YEAR)
5.3.1.c Gender
5.3.1.d Race
5.3.1.e Five-digit zip code
5.3.1.f Ethnicity
5.3.1.g Caregiver's preferred and alternate phone numbers (and email address if patients consent to be contacted via email)

6.0. Intervention

The original SICP intervention included clinical tools, training, and system changes (Table 1). The primary clinician tool was a structured communication guide called the Serious Illness Conversation Guide (SICG; https://www.ariadnelabs.org/wp-content/uploads/sites/2/2017/05/SICG-2017-04-21_FINAL.pdf). We conducted 45 qualitative interviews with oncology clinicians, palliative care clinicians, patients with hematologic malignancies, and their caregivers to adapt the original SICG. Our adapted SICG is designed to meet the unique needs of older patients with hematologic malignancies. The adapted SICG was further refined based on feedback gathered through APP focus group interviews (Aim 1).

Table 1 SICP intervention components and description

Intervention Component	Description
Clinical tools	
SICG	The SICG was used by intervention clinicians to guide the conversation. SICG is a structured communication guide that provides clinicians with psychologically informed language to assess illness understanding and patient information preferences; share prognosis according to patient preferences; explore patient values, goals, and care preferences; and make a recommendation based on patient priorities.
Patient and family materials	Intervention patients were prepared ahead of the conversation with a written letter; patients were also given a Family Guide after a SICG conversation to support follow-up discussions with their family members.
Clinician training	
Skills-based training program of 2.5 hours	Structured training was delivered to intervention clinicians with standardized elements and individualized observation and feedback delivered by palliative care faculty.
System changes	
Patient identification using the "surprise question"[a]	The surprise question "Would you be surprised if this patient died in the next year?"[33] was applied at regular intervals by oncology clinicians to lists of their patients.
Reminders	Email reminders were provided to intervention clinicians to initiate conversations using the SICG during routine care visits in the outpatient setting.
SICG documentation template in an accessible advance care planning module in the EMR	A novel, structured, accessible template in the electronic medical record was developed to document serious illness conversations, and intervention clinicians were trained to use it.
Coaching on use of the SICG	Palliative care faculty offered coaching to intervention clinicians on use of the SICG by phone, email, or in person.

Table 2 Adapted SICG for patients with hematologic malignancies.

Serious Illness Conversation Guide

CONVERSATION FLOW

1. **Set up the conversation**
   - Introduce purpose
   - Prepare for future decisions
   - Ask permission

2. **Assess understanding and preferences**

3. **Share understanding**
   - Share prognosis if appropriate
   - Frame as a "wish", "hope" statement
   - Allow silence, explore emotion

4. **Explore key topics**
   - Values/Goals
   - Worries or Fears
   - Strength
   - Tradeoffs
   - Caregiver and family

5. **Close the conversation**
   - Summarize
   - Make a recommendation
   - Welcome suggestions
   - Check in with patient
   - Ask for involvement of caregiver and family
   - Affirm commitment

6. **Document your conversation**
   - Consider creating a note that is separate from the daily progress note
     OR
   - Consider documenting conversation at the beginning or end of a daily progress note

7. **Communicate with key clinicians**

Serious Illness Conversation Guide

SET UP

- "Many patients like to talk about what is ahead with their illness and think about what is important to them. This is part of the care we provide for <u>all of our patients</u> to make sure that we provide the care you want – **is this something you would like to talk about?**"

ASSESS

- "What is **your understanding now** of where you are with your illness?" (*ask if patient understands the plan for their cancer*)
- "What kind of **information would you like to know** about what is ahead with your illness?"
- "I want to share with you **my understanding** of where things are with your illness – is that something you [and others] would like to know"

SHARE (CHOOSE ONE)

- <u>*Uncertainty:*</u> "It can be difficult to predict what will happen with your illness. I **hope** you will be able to live the life you want, but and it is possible that you could get sick quickly or *may have to stay in the hospital longer*. I think it is important to prepare for that possibility."

OR

- <u>*Prognosis:*</u> "I **wish** we were not in this situation, but it is possible that time may be as short as [*express as a range, e.g. days to weeks, weeks to months, months to a year*]."

OR

- <u>*Functional status:*</u> "I **hope** this is not the case, but patients in your situation may have more physical difficulty in the upcoming [*days, weeks, years*]. It is possible that things may get harder for you."

EXPLORE

- "What is most **important** to you (**goal**) if your health worsens?"
- "Do you have any **worries or fears** about your health? If so, what worries you the most?"
- "What gives you **strength** as you think about the future with your health?"
- "If you become sicker, what are you **willing/not willing to go through** for the possibility of living longer?"
- "Is there something that is really important for me to understand about you?"
- "I know you have been in the hospital for [*days, weeks*], have your spoken with your **caregiver/family** about your feelings regarding your illness?

CLOSE

- "I've heard you say that _____ is really important to you. I would like to share my recommendations based on what we have talked about – is this okay?
- Keeping that in mind, and what we know about your illness, I **recommend** that we____. This will help us make sure that your treatment plans reflect what's important to you."
- "Would you like to add anything to that?"
- "We could have a meeting with your caregiver/family and talk more about this."
- "I care about what happens to you and I will continue to help you through this."

7.0. Treatment Protocol

7.1. Study Outline

For Aim 1, we will identify all inpatient APPs. We will email the intervention materials to them before the focus group meetings. Following this, the study team will conduct in-person or zoom/phone focus group interviews with APPs for 30-60 minutes. First, we will explain the rationale of the study. Second, we elicit preferences and feedback regarding the inpatient APP-delivered ACP intervention. This will include preferences on SICG training (i.e., length of training, in-person vs. virtual, live vs. prerecorded) and on SICG implementation (i.e., organization and content of the SICG including language that should be added, removed, or changed, workflow).

For Aim 2, we will screen and consent eligible patients of treating physicians at WCI. After consent, the study subject and caregiver (if applicable) will complete demographics and baseline measures. The patient will be provided with the "Patient Preparation Letter" following completion of baseline measures and prior to the inpatient ACP visit. This will allow the patient to review the document and prepare for their discussion with the APP/hematology/oncology fellow. Following this and during the same hospital admission, an inpatient ACP visit will be scheduled with an APP/hematology/oncology fellow on the inpatient malignant hematology service. The APP/hematology/oncology fellow will use the "Serious Illness Care Guide" during this visit with the patient. The APPs who participated in Aim 1 of this study have already completed training on how to use this guide. For additional APPs who may join in Aim 2 and hematology/oncology fellows who will join in Aim 2, they will complete the same training session as the original group of APPs on how to use this guide. Finally, at the end of the visit, the patient will be provided with the "Family Guide" (either from the APP/hematology/oncology fellow or the study coordinator). The patient can use this guide to help communicate with their family about the visit that they had with the APP/hematology/oncology fellow. The APP/hematology/oncology fellow will be able to access with the Epic Serious Illness Conversation Template on Epic and will document their conversation with the patient using the template in the electronic medical record.

During the ACP visit, the APP/hematology/oncology fellow will discuss ACP and EOL care. This visit will be recorded. After the visit, the study subject and caregiver (if applicable) will complete post-intervention measures. Within 4 weeks of the in-patient visit, we will conduct an interview with the patient and caregiver (if applicable) either in-person or via zoom/phone for 30-60 minutes. We will also conduct an interview with the APPs/hematology/oncology fellows who participated in the ACP visits with the patients at the end of the study. All parties present for the recorded visit, including enrolled patients, any accompanying caregivers, family or friends, the APP/hematology/oncology fellow, and any other physicians or health care providers not participating in the study will be fully aware that the conversation is being audio- recorded before any recording begins, in addition to the prior written consent of enrolled patients. Patients, caregivers, and APPs/hematology/oncology fellows may request access to the audio recording or the written transcript.

In order to collect data from the EMR regarding EOL metrics, patients in this study will be followed until death or up to 5 years following their participation.

7.2. Assessments of the Participants

Demographic, clinical, and cancer characteristics will be collected on paper or via RedCap**.**

7.2.1. Demographics (APPs, Fellows, Patient, and Caregivers)

APPs/hematology/oncology fellows age, race, ethnicity gender, and years in practice since completion of training will be collected. For hematology/oncology fellows, years in fellowship will be collected.

Patient and caregiver's age, race, ethnicity, gender, highest level of education achieved, employment status, and marital status. Caregiver's relationship to the patient will also be inquired. This will only be collected at baseline.

7.2.2. Clinical and Cancer Characteristics (Patient)

ECOG performance status, comorbidities, medications, weight, height, BMI, diagnosis and date of diagnosis, prior hematologic malignancies, stage/risk group, and treatment regimen will be abstracted from the medical records. This information will only be collected at baseline.

In addition, we will collect the following from the medical records (up to 5 years following their participation in the study or death) which will provide end of life quality indicators. We have previously collected this information in a retrospective fashion and will use similar procedures to extract this information prospectively from the medical records.

- Hospice enrollment (and timing relative to death)
- Palliative care referral (and timing relative to diagnosis)
- Chemotherapy administration within the last 2 weeks of life
- Completion of advance directives which include MOLST forms, living will, durable power of attorney for healthcare, and healthcare proxy forms (and timing related to diagnosis and death)
- Do not resuscitate order /Do not intubate order (and timing related to diagnosis and death)
- Emergency department visits in the last 30 days of life
- ICU admissions in the last 30 days of life
- Hospitalization in the last 30 days of life (number of hospitalizations, reasons for hospitalizations)
- Use of life-sustaining treatments (e.g., mechanical ventilation, vasopressors,

tracheostomy, dialysis for acute kidney injury, percutaneous endoscopic gastrostomy) in the last 30 days of life
- Transfusion in the last 7 days of life
- Place of death (home, hospital, facility, etc.)
- Inpatient mortality rate

7.2.3. Measures

Measures will be collected via in-person, done via email on redcap as a survey option, or from mailings sent to the participants.

7.2.3.1. Functional Status (Patient) – baseline only – Aim 2

Activities of daily living (ADL): ADLs are measures of self-care. ADL independence will be assessed using the Katz Index of Independence in Activities of Daily Living, commonly referred to as the Katz ADL. The Katz ADL is the most appropriate instrument to assess functional status as a measurement of the client's ability to perform activities of daily living independently. Clinicians typically use the tool to detect problems in performing activities of daily living and to plan care accordingly. The Index ranks adequacy of performance in the six functions of *bathing, dressing, toileting, transferring, continence, and feeding.* Clients are scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment.[22]

Instrumental Activities of Daily Living (IADL): Self-reported functional status will be assessed using the IADL subscale of the Multidimensional Functional Assessment Questionnaire: Older American Resources and Services (OARS). The IADL subscale consists of seven questions rated on a three-point Likert scale. It measures the degree to which an activity can be performed independently.[23]

Fall History: A self-reported history of falls in the past year will be recorded. A history of a recent fall has been demonstrated to be independently predictive of increased risk for chemotherapy toxicity in older cancer patients.[24]

7.2.3.2. Nutritional status (Patient) – baseline only – Aim 2

Self-reported weight loss in the past 6 months.

7.2.3.3. Social Support (Patient) – baseline only – Aim 2

Patients self-report their living situation and their main social support.

7.2.3.4. Psychological Health (Patient and Caregiver) – baseline only – Aim 2

Geriatric Depression Scale-15: A 15-item screening instrument for depressive symptoms in older adults.[25]

7.2.3.5. Cognition (Patient) – baseline only – Aim 2

Mini-Cog (baseline only): Brief, cognitive screening test that is used to evaluate cognition in older adults.[26]

7.2.3.6. Health Literacy (Patient) – baseline only – Aim 2

Cancer health literacy (CHLT-6): A brief instrument to determine whether an individual has limited cancer health literacy.[27]

7.2.3.7. Disease Understanding (Patient) – baseline and post-intervention – Aim 2

Disease Understanding – Patient: A questionnaire assessing patient's prognostic understanding of illness. They will also be asked if prognostic information was provided.

7.2.3.8. ACP Engagement Survey (Patient) – baseline and post-intervention – Aim 2

ACP Engagement Survey: 15-item engagement survey that assess patient self-efficacy and readiness for identification of a medical decision maker, identification of personal values, and flexibility in decision making and communication with their physician.

7.2.3.9. ACP Documentation – baseline and post intervention – Aim 2

Data on ACP documentation will be collected through the electronic medical record. This will include explicit statement of the patient's medical preferences for EOL care in a note, scanned MOLST form that was completed with their clinician, and/or scanned healthcare proxy form that was completed with their clinician.

7.2.3.10. Acceptability Questionnaire (Patient and APP/Fellow) – post-intervention only – Aim 2

Patient Acceptability Questionnaire (Aim 2): A questionnaire used in the original

evaluation of the SICP implementation to assess the impact of the serious illness conversation on the patient's understanding and perception of their diagnosis.[28]

Clinician Confidence Questionnaire (Aim 2): A questionnaire used in the original study evaluating the SICP implementation to assess clinician's self-perceived ability to implement the SICP in real practice. This will be used in Aim 2 at 3 time points: before the SICP training (led by Dr. Thomas Carroll), after the SICP training, and at completion of the study (APPs and hematology/oncology fellows will complete the same training).[27]

Clinician Acceptability Questionnaire (Aim 2): A questionnaire used in the original study evaluating the SICP implementation to assess the clinicians experience in using the SICP with patients.[27]

7.2.3.11. Feasibility metrics

Feasibility metrics will be collected:

- Retention rate (percentage of patients consented to the study ultimately completing all study components) – primary metric
- Recruitment rate (percentage of patients who are approached and agree to enroll) will also be described.

8.0. Data Handling and Statistical Considerations

8.1. Data Handling

8.1.1. The same protocols and procedures for data quality and control that are readily used for the NCI Community Oncology Research Program (NCORP) Research Base protocols currently being overseen by our office (which have accrued over 1,000 patients in the previous year) will be used for this study. Patients will fill out forms generated from RedCap and this information will be entered into RedCap (Section 9.5). They may also complete RedCap survey directly. Study personnel will perform Mini-Cog and the scores will be entered into RedCap.

8.1.2. It is anticipated that allowing for the appropriate number of evaluable participants and by checking self-report measures for completeness, we will have a full complement of data. Every effort will be made to encourage and facilitate participants' completion of all questionnaires and all items on the questionnaires for each study assessment. In the event that missing data occur, every effort will be made to contact participants via phone and obtain the data or to find out why the questionnaires or items are missing. The reasons for missing data will be documented. Missing questionnaire items will be treated in accordance with the documented scoring procedures. Although it is very unlikely that missing values will not occur randomly, we will confirm their randomness. Multiple imputation[29] will be

applied to (1) give more accurate statistical tests and standard errors for key treatment effect parameters and to (2) give some indication of the sensitivity of the analyses to missing data. The causes and pattern of the missing data will be examined and taken into consideration in the design of future studies.

8.1.3. For audio-recordings, these will be uploaded to Box within a week of the interview/clinic visits and deleted from the digital audio recorder (Sony). The recordings will be transcribed by a professional transcription service, and the transcripts will be used for data analysis.

8.1.4. Data collected (both assessments and transcripts) will only be accessed by the following: 1) The research team and 2) The treating physician (only if the patient consents for research information to be shared or if their treating physician is a study co- investigator).

8.2 Data Analysis and Sample Size:

8.2.1 Analysis Plan for Aim 1

Qualitative analyses: We anticipate thematic saturation will be reached with this number (N=approximately 10-15) of participants based on previous studies (i.e., the point at which no new data emerge).[16,17] All interviews will be conducted and audio-recorded by study personnel and then transcribed by a professional transcription service. Two trained personnel ("coders") will extract and highlight themes from the transcripts. We will analyze the qualitative data using grounded theory and constant comparative methods, with coding to structure data into categories and create groups according to the broader issues or themes.[31] The themes will focus on feedback on training materials (e.g., prerecorded vs. interactive sessions, duration of training) and processes (e.g., workflow, template to document ACP visit in the electronic medical record) in the inpatient setting. These interviews will be audio-recorded by study personnel and then transcribed. We will keep an audit trail to establish trustworthiness. We will critically examine the data collection and analysis process, discuss emerging codes, and reach consensus on principal themes. These themes will be used to adapt the inpatient APP/fellow-delivered ACP intervention.

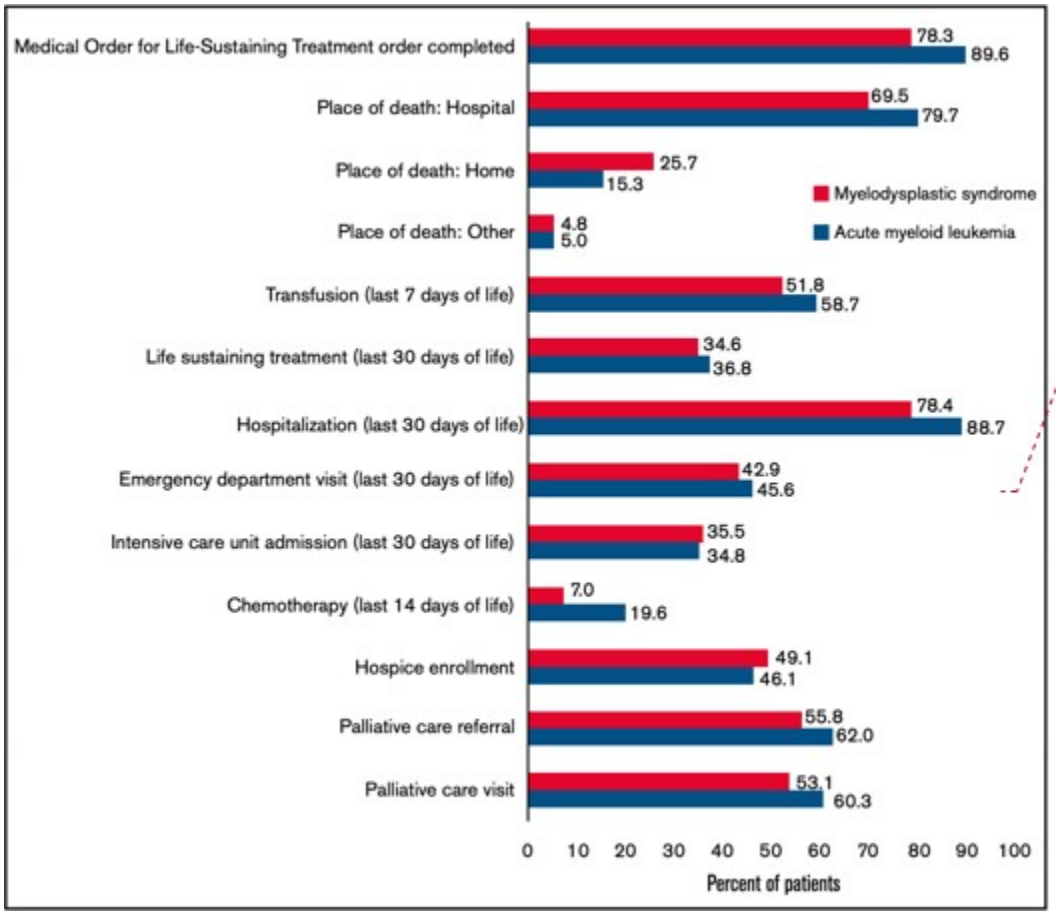
8.2.2 Analysis Plan for Aim 2

Quantitative analyses: We will use descriptive statistics to summarize feasibility metrics and all measures. Feasibility will be defined based on the retention rate (% of patients approached who consented and complete the ACP visit); >70% will be considered a successful benchmark for feasibility. Rates will be presented with associated two-sided 95% exact binomial confidence

intervals. A sample size of 50 patients produces a confidence interval with a maximum width of 0.29 (limits 0.36-0.65), when the observed feasibility rate is 0.50. We anticipate a higher feasibility rate, which will result in a narrower confidence interval. If the observed feasibility rate is 0.70, the width of the confidence interval is reduced to 0.24 (limits 0.55-0.82). If more than 50 patients are approached, then the confidence intervals will become narrower. Recruitment rate will be the % of patients approached who agree to participate (i.e., consent), and will be described similarly.

Models for comparison with historical control: For AML and MDS specifically, we will compare outcomes (EOL quality indicators) to a historical control cohort, which we have previously collected and published.[12] Rates of EOL outcomes in the historical cohort are shown in Figure 4, and range from <20% (chemotherapy in the last 14 days of life) to >80% (hospitalization in the last 30 days of life). Rates of EOL outcomes in this study population will be graphically summarized in a similar fashion. We aim to compare EOL outcome measures in this study population to EOL outcomes seen in the historical cohort referenced above.

Figure 1: End of life quality indicators (2014-2019)



Qualitative analyses: All inpatient ACP visits and interviews will be audio-recorded by study personnel and then transcribed by a professional transcription service. Inpatient ACP visit transcript themes will focus on the APPs/hematology/oncology fellows ability to assess EOL concerns brought up by the patient and caregiver, as well as advance directive completion. Post-intervention interview themes will focus on participant experience during the inpatient ACP visit and feedback which will be used to further optimize the study procedures and intervention.

9.0 Data Management

9.1. Data Collection Table

9.1.1. Aim 1

a) APP

	Eligibility and consent form	Baseline Assessment	Post-Interview Assessment
Informed Consent	X		
Demographics		X	
Focus Group Interview		X	

9.1.2. Aim 2

a) APP/Hematology/Oncology Fellow

	Eligibility and consent form	Baseline Assessment	Post-Intervention Assessment
Informed Consent	X		
Demographics		X	
Qualitative Interview			X (at the end of the study)
Clinician Acceptability Questionnaire			X
Clinician Confidence Questionnaire		X (before and after SICP training)	X (at the end of the study)

b) Patient

	Eligibility and consent form	Baseline Assessment	Post-Intervention Assessment
Informed Consent	X		
Demographics		X	
Clinical and Cancer Characteristics		X	
Cancer Health Literacy (CHLT-6)		X	
Disease Understanding		X	X
Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Fall History		X	
Nutritional Status		X	
Geriatric Depression Scale-15		X	
Mini-Cog		X	
ACP Engagement Survey		X	X
Qualitative Interview			X
Patient Acceptability Questionnaire			X
End-of-Life Quality Indicators			X (up to 5 years or death; EMR)

c) Caregiver (if applicable)

	Eligibility and consent form	Baseline Assessment	Post-Intervention Assessment
Informed Consent	X		
Demographics		X	
Qualitative Interview			X
Acceptability Questionnaire			X

9.2. All hardcopy research records will be stored onsite in the URMC, in locked research files at the Wilmot Cancer Institute (WCI). The Cancer Center is secured with electronic key cards. Offices within the Cancer Center are again secured by key and data is kept in locked file cabinets. Electronic research records are stored on the URMC's password secured and firewall

protected networks. These are the same methods of security used for patient medical records. For audio-recordings, these will be uploaded to Box within a week of the interview and deleted from the audio recorder. All study data will be kept for a period of 7 years after the study and all reports and publications are complete.

9.3. All data collected for the current study will be used in post hoc analyses as appropriate. Data will not be used for future studies without prior consent of the patient. The patient's individual research record will not be shared with their treating physician, unless they provide consent or the patient's treating physician is a study physician, in which case they will have access to study data as a study co-investigator. Overall study results will be presented to participants, faculty and staff at the URMC after completion of the study. Study results will be presented at professional meetings and published.

9.4. The study coordinator will assign a numerical study ID to each participant once they have signed the consent form (chronologically based on the data they signed consent i.e., 001, 002, 003…). All study forms and questionnaires will use this number and the participant's first, middle, and last initials as identifiers, to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with study ID, name, and contact information will be maintained separately. This linkage information will only be accessible to the study coordinator, study investigators, and the individuals responsible for maintaining the database.

9.5. Additionally, data on the socio-demographics, clinical, and cancer and treatment characteristics will be collected and managed by the research teams at URMC using REDCap electronic data capture tools hosted at URMC.[32] We will also evaluate the medical records for clinical characteristics and outcomes, and utilize REDCap to collect and manage this information.

> 9.5.a. URMC provides the following information on the REDCap program: "Vanderbilt University, in collaboration with a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data, called REDCap (Research Electronic Data Capture). The REDCap system is a secure, web-based application that is flexible enough to be used for a variety of types of research. It provides an intuitive interface for users to enter data and real time validation rules (with automated data type and range checks) at the time of data entry. REDCap offers easy data manipulation with audit trails and functionality for reporting, monitoring and querying patient records, as well as an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Through the REDCap Consortium, Vanderbilt has disseminated REDCap for use around the world. Currently, over 240 academic and non-profit consortium partners on six continents with over 26,000 research end-users use REDCap.[33]
>
> 9.5.b. According to the Clinical and Translational Science Institute (CTSI), REDCap is

supported with the following means. “The *CTSI Informatics Core*, a unit of the SMD *Academic Information Technology (AIT) Group,* will serve as a central facilitator for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team, with planning assistance from the *AIT-CTSI Informatics Core*. The iterative development and testing process results in a well-planned data collection strategy for individual studies.[31]

9.5.c. The CTSI states that regarding security, “REDCap servers are housed in a local data center at the University of Rochester and all web-based information transmission is encrypted. REDCap was developed in a manner consistent with HIPAA security requirements and is recommended to University of Rochester researchers by the URMC Research Privacy Officer and Office for Human Subject Protection.[33]

10.0 Risks/Benefit

10.1. Risks

There is potential loss of confidentially associated with participation in the proposed study. In terms of loss of confidentiality, quantitative data from participants will need to be stored. Though rigorous and well-tested data safety and security guidelines will be observed, there is still a chance that confidentiality could be breached, and sensitive medical information could become known to persons outside the research team.

Advarra will be used as the direct payment system for study payments. During registration or account creation on the site, Advarra may collect any or all of the following subject information, (i) name, (ii) home or business address, (iii) professional information, including specialty or nature of concern, (iv) organization with whom they are affiliated and its address, and (v) email address. When they visit the site using their personal smart device, the site may automatically record information that their browser sends like, the name of the domain and host from which they access the Internet; the Internet Protocol (IP) address of the computer or smart device they are using; the date and time they access the site or make uploads or post to the site; and the Internet address of the website from which they linked directly to the site. This information does not include any Personally Identifiable Information and we refer to this information as non-identifiable information.

There is still a risk that a third party could gain access to any Information provided to or collected through this site. To mitigate these risks, any data breaches and, potential identification of the subjects, Advarra has security measures in place to protect electronically transmitted information. They are frequently reviewing and consistently trying to improve the security of the site. They do not collect and subjects will not be asked to submit any "protected health information" as defined in HIPAA.

10.2. Benefits

There are no anticipated benefits to the participants.

10.3 Payments and Costs

Patients and caregivers participating will be paid $10 for their participation in the form of gift cards following their inpatient APP/hematology/oncology fellow-delivered ACP visit. APPs/hematology/oncology fellows will not be reimbursed for their participation. However, for APPs, if we have to schedule the training on how to deliver the ACP intervention outside of the APP working hours, they will be paid for those working hours by the APP leadership (confirmation with APP leadership through email communication). There are no additional costs to patients and caregivers for participating in this study.

For this study we will use a subject payment system called Advarra Participant Payments. The system allows three ways to provide payment. Subjects can choose: a reloadable debit card; direct deposit; or mailed paper checks. The study team will help create a "subject profile" in the system. In order to provide payment, the subject will need to enter their name and date of birth into their subject profile. Depending on which payment method they choose, they may also need to enter their email address and banking information. If the subject already has an Advarra account (because of another study that uses this system), the existing profile will be used to provide payment.

10.4 Future Work

Results of this study can be expanded to guide ACP interventions for other types of cancers. It can also be translated to other languages.

11.0. DATA SAFETY AND MONITORING

Only adverse events (AEs) related to the study intervention or procedures will be reported. In other words, AEs related to cancer treatment will not be reported.

11.1. Adverse Event Reporting Requirements

11.1.1. Adverse events will be reported using the URCC Adverse Event form and/or as required by the Cancer Center Clinical Trials Office.

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
		Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
	Unexpected and Expected	with hospitalization	without hospital-ization		with hospitalization	without hospitalization	with hospitalization	without hospitalization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days
Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.												

11.1.2. Adverse events will be reported in accordance with the following guidelines:

11.1.3. Adverse event reports will be submitted in one of the following ways:

(1) By email: (pdf)

(2) By mail:

(3) By fax:

11.1.4. An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risk information. This is a minimal risk study as both exercise and mobile app-driven interventions have been shown to improve outcomes in community-dwelling older adults. If study bone marrow biopsy is collected, this would be a greater than minimal risk study.

11.1.5. A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. We anticipate that any serious events will be related to standard of care cancer treatments and not due to the intervention. We will not collect adverse events related to cancer treatments.

11.1.6. Adverse events will be reported in accordance with institutional policies (University of Rochester, Research Subject Review Board, local IRB, URCC CCOP, CTO, and DSMB) as per their requirements.

11.2. Data Safety Monitoring

11.2.1. All adverse events requiring reporting will be submitted to the current Project Coordinator as described in Section 11.1. Serious adverse event reports will be forwarded to the study chair and the Data Safety and Monitoring Committee (DSMC). Adverse events are entered into a protocol-specific spreadsheet.

11.2.2. Adverse event rates are monitored utilizing the spreadsheet. If a serious adverse event is reported frequently, the study chair will conduct a detailed review. The DSMC Committee Chair will be notified and will determine if further action is required.

11.2.3. The Data Safety Monitoring Committee (DSMC) will review study progress and cumulative reports of adverse events every year and as needed. An overall assessment of accrual and adverse events will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure.

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