# LCCC 2136: Understanding What Matters Most to Patients: Establishing the Validity of a Best-Worst Scaling Survey

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**Sponsor**: Lineberger Comprehensive Cancer Center

**Funding Source**: Palliative Care Research Consortium Pilot Award

**Version Date: 1.0 September 1, 2021**

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## Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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**PI Signature: _____**

**Date:_____**

**Version Date:_____**

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# 1.0 BACKGROUND AND RATIONALE

## 1.1 Study Synopsis

This study will evaluate the content validity of using a survey to quantify patient preferences at the point-of-care for newly-diagnosed patients with hematologic malignancies. Our primary hypothesis is that by identifying the strength of patient preferences for outcomes with this survey, clinicians will be able to improve goal-concordant care by aligning clinical recommendations with patients' preferences. We will conduct cognitive interviews with 20 patients to establish the content validity of the survey. We will use purposive sampling based on the results of the survey to create two groups of patients (n=10 each) for the cognitive interviews. We plan to recruit 50 total patients to complete the survey to ensure adequate recruitment in each group. Secondary outcomes will evaluate acceptability and feasibility of administrating the survey. The information we obtain from these participants will be used to refine the survey. Interviews with oncologists and palliative care specialists (up to 10) will inform implementation.

## 1.2 Background

Treatment decisions in oncology are increasingly preference sensitive. Cancer patients differ substantially in their preferences for achieving various outcomes.[1–3] For example in AML, we have shown that some patients prefer to maximize their overall chance of long-term survival and are willing to endure a high burden of side effects or a lengthy hospitalization for this opportunity; others prefer to minimize treatment effects in order to maintain their quality of life.[1] As more therapies are becoming available across oncology, this preference heterogeneity suggests that treatment decisions will increasingly become preference sensitive—ideal therapy choice will depend on patients' preferences for treatment outcomes.

Routine shared decision-making (SDM) is currently inadequate to reliably capture patient preferences.[4–8] Multiple systematic reviews have demonstrated consistent discordance after routine SDM between physician perceptions of what matters most to patients and patients' stated preferences.[8,9] A recent evaluation of a clearly preference-sensitive decision in oncology demonstrated that about half the time oncologists did not elicit patient preferences.[10] Analyses of the quality of SDM in leukemia, for example, demonstrate a high rate of patient dissatisfaction with communication and very poor patient-provider concordance on goals and prognosis.[11–13] As a stark example of patient-provider discordance following routine SDM, 80% of leukemia patients receiving symptom-directed therapy believe they are likely to be cured, when less than 5% will be.[14] Palliative care clinicians can serve to improve these outcomes, but often have limited bandwidth to see most patients.

Preference elicitation instruments can capture patient preferences, however fundamental challenges remain to their implementation in complex clinical care. Numerous stakeholders including the FDA strongly advocate for patient

preferences to be integrated into SDM and clinical care.[15–18] Preference elicitation instruments that were originally developed in economics to understand consumer behavior are increasingly being applied in healthcare to identify outcomes that are most valued by stakeholders. These instruments allow researchers to understand the relative importance of a group of items (attributes) to a population based on a series of choice tasks.[19–21] In clinical trials evaluating dichotomized decisions where the risks and benefits of treatment options are well-established, these instruments have been shown to improve patient satisfaction, increase high-quality decisions, and align treatment choice with risk.[2,22–25] Fundamental questions remain, however, about how to assess and apply preference data to complex SDM in advanced cancer patients where risks and benefits of available options vary for each patient.[26–28] Further, substantial methodological barriers exist in assessing individual preferences over time and pose a critical challenge to longitudinal goal-concordant care. To address these critical gaps, we will use treatment decisions for patients with hematologic malignancies as the context for developing generalizable strategies to improve the goal-concordance of complex treatment decisions in palliative care/oncology.

### 1.3 Purpose and Rationale

In this study, we will recruit older ($\geq$ 60 years) participants with newly-diagnosed hematologic malignancies to complete the BWS survey and provide quantitative and qualitative feedback to validate the survey. Interviews with a sample of oncologists and palliative care physicians will be completed to identify barriers and facilitators to implementation of the survey into routine clinical care.

## 2.0 STUDY OBJECTIVES AND ENDPOINTS

### 2.1 Primary Objective

To evaluate the content validity of using a BWS survey to quantify the preferences of older patients with hematologic malignancies at the point-of-care.

*Content Validity*: Content validity will be assessed in cognitive interviews with participants. We will first assess the respondent's comprehension of the questionnaire and its items in relation to their intended meaning. We will identify any formatting or wording difficulties with the survey itself. Next, we will evaluate participants comprehension of the content by use of probing questions to evaluate if other important aspects of treatment decision-making were absent in the survey.

### 2.2 Secondary Objectives

1. To report the acceptability of the BWS survey to patients. This will be defined as participants answering agree/strongly agree to “I found the survey acceptable to clarify my preferences”.

2. To report the preliminary efficacy of the BWS survey to improve goal-concordant care. This will be defined as participants answering "moderately effective/very effective" to the question: "How effective was the survey to help you and your doctor choose a treatment that was consistent with your goals?"

3. To report on completion rate over time. This will be reported by the number of patients who complete the BWS survey at each timepoint across the study.

### 2.3 Exploratory Objectives

1. [redacted]

## 3.0 PARTICIPANT ELIGIBILITY

### 3.1 Inclusion Criteria

Patients must meet all of the inclusion criteria listed below to participate in the study.

- have a confirmed new diagnosis of the following hematologic malignancies:
  - Aggressive lymphoma (including, but not exclusive of, diffuse large B-cell lymphoma, advanced stage Hodgkin's lymphoma, Burkitt lymphoma, double hit lymphoma, mantle cell lymphoma)
  - multiple myeloma
  - chronic lymphocytic leukemia
  - chronic myeloid leukemia
  - acute myeloid leukemia
  - acute lymphoblastic leukemia
  - myelodysplastic syndrome with excess blasts (MDS EB1 or MDS EB2)

- Age $\geq$ 60
- Ability to read, understand, and communicate fluently in English
- Ability to understand and comply with study procedures

- Willingness and ability to provide written informed consent

Patients will become eligible for enrollment upon pathologic confirmation.

Patients will be eligible for enrollment for 28 days after confirmatory diagnosis or until the start of chemotherapy.

Chemotherapy will not include hydroxyurea, cyclophosphamide, or cytarabine if used only for emergent cytoreduction.

Health care clinicians must be employed in hematology/oncology or palliative care as a nurse navigator, advanced practitioner, and/or physician. Together, these participants will be referred to as healthcare clinicians.

### 3.2 Exclusion Criteria

All subjects meeting any of the exclusion criteria listed below at baseline will be excluded from study participation:

3.2.1 Dementia, altered mental status, or psychiatric condition that would prohibit the understanding or rendering of informed consent or participation in the discrete choice experiment.

3.2.2 Significant medical conditions, as assessed by the investigators, that would substantially increase the burden on the patient to complete study assessments (such as multiorgan failure, respiratory failure, or other critical illness).

## 4.0 STUDY PLAN

### 4.1 Schema

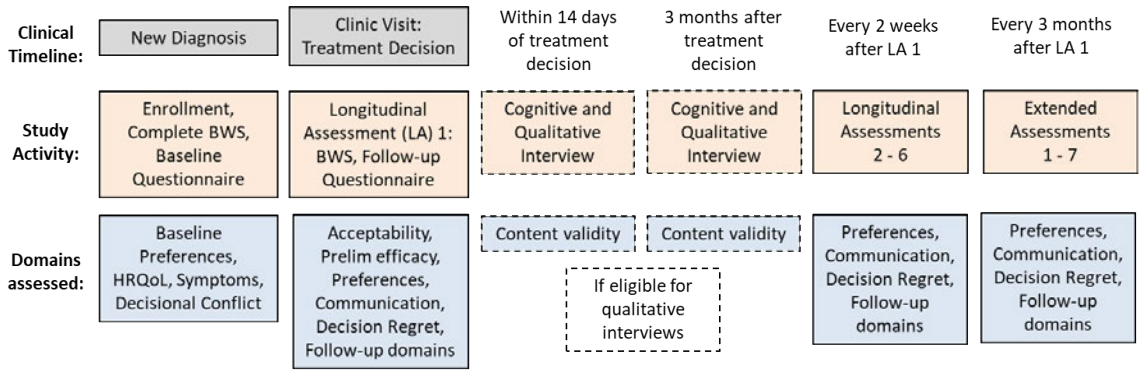
4.1.1 This study will evaluate the validity of using this out(BWS) survey to quantify patient preferences at the point-of-care and the potential effectiveness of the survey to improve goal-concordant care. Our primary hypothesis is that by identifying the strength of patient preferences for outcomes with this survey, clinicians will be able to improve goal-concordant care by aligning clinical recommendations with patients' preferences.

Within this study we aim to evaluate the content validity, acceptability, and potential effectiveness of the BWS survey to improve goal-concordant care. Using the BWS survey, we will collect the preferences of 50 older (>60 years) newly-diagnosed hematologic cancer patients facing treatment decisions and evaluate content and construct validity of the survey, patient acceptability, and

effect of preference elicitation on patient-reported quality of treatment decisions (effectiveness). Qualitative interviews involving cognitive interview questions (n=20) with patients will further explore the content validity of the survey and potential effect of the surveys on goal-concordant care. Interviews with palliative care clinicians, and oncologists will explore barriers and facilitators of implementation.

We also aim to describe how patients' preferences change over time and explore potential relationships between patients' preferences and clinical outcomes. We will collect the preferences of the patients with hematologic cancer every other week for 3 months (repeat sampling up 5 times) and then every 3 months thereafter for up to 2 years. We will describe changes in preferences at each timepoint. An exploratory, hypothesis-generating analysis will evaluate correlations between preferences and standard clinical outcomes (e.g. treatment intensity and response), symptoms (collected with the PRO-CTCAE), health-related quality of life (EQ-5D), and decisional satisfaction to provide direction for future studies.

### 4.1.2 Trial Schema outline (patients)




## 4.2 Duration of Study

The recruitment is planned to last for up to 24 months. Patients will complete the survey instruments up to 6 times over 3 months (Longitudinal Assessments) and then every 3 months for up to 2 years (7 times) (Extended Assessments). Patients will complete qualitative interviews within 3 months of treatment decision. Clinicians will be interviewed once over the course of the study.

## 4.3 Study Details

4.3.1 The study will recruit 50 total participants and conduct qualitative interviews on a subset of 20 participants.

4.3.2 **Pilot testing:** The study team will review the inpatient census and clinic schedule to evaluate for potentially eligible patients. The study team will confirm patient eligibility with the primary oncologist or principal investigator. Eligible patients will be sequentially approached to be recruited to this study until 50 patients are recruited who complete BWS survey.

Upon enrollment, the study team will record information about patients obtained from the patient or the medical record including gender, age, lab values including complete metabolic profile, complete and diffentiated blood counts, albumin, LDH, a1c, cholesterol levels, hematopathology reports, clinician-determined performance status (Karnofsky and ECOG), and comorbidities present. Demographic information such as age, sex, and zip code will be obtained.

Once consented, patients will complete initial study questionnaires within PRO Core either remotely if able or in-person with the assistance of study staff prior to a clinic visit. For patients who decline to participate in the study, reasons for refusal will be anonymously collected to examine the issue of selection bias as well as to assist with determination of feasibility.

After the clinic visit, patients will be prompted to complete the first longitudinal assessment via PRO Core. This will be available for 7 days. The treating oncologist who saw the patient will be prompted to fill out an assessment via email. Clinicians may receive multiple reminder emails to complete the survey to improve completion rates. We will collect provider responses within 2 weeks of initial patient survey.

Following, every 2 weeks (up to 5 times) participants will be prompted in PRO Core to complete the longitudinal assessment survey. Then, the extended assessment survey will be delivered by PRO Core every 3 months for up to 2 years (7 times).

<u>Retention</u>:

Multiple strategies will be utilized to retain patients on study.
1. *Provide Detailed Rationale of the Study and Study Brochure*: Upon enrollment participants will be informed of the rationale of the study: to help understand what is most important to each patient to tailor therapy to patient preferences. Patients will be informed that their responses will help adapt the survey that they will receive to help future patients. They will be given printed information about the study if recruitment is done in person.

2. *Training*: Each patient will receive training on how to complete the assessments in PRO Core. This will take place during enrollment (either in person or remotely).
3. *Reminders to complete the initial post-visit assessments*: The day after the treatment encounter, patients will receive an automated reminder to complete the assessments.
4. *Reminders to complete the follow-up assessments*: Staff will direct them to complete the assessment remotely via a secure link sent by email. PRO Core will send patients a reminder daily for up to 2 days in case of non-response. Study staff will call patients if no response.
5. *Reminders in case of non-response*: Study staff will call patients if no response.
6. *Support to complete assessments*: Staff will assist participants to log-on to PRO Core and to complete assessments if needed.
7. *Compensation*: Participants will be provided with a $10 gift card following completion of each longitudinal and extended assessment.

4.3.3 **Qualitative Interviews:** Based on responses to the survey, 20 patients will be selected to complete interviews. Patients will complete an initial interview and a follow-up interview.

The study team will review patients who have consented to the study and confirm eligibility with the primary oncologist or principal investigator. Study staff will call eligible patients to participate in the interviews until the number of desired participants has been reached (n=20) according to the inclusion criteria above and recruitment goals below.

We will use purposive sampling to stratify participants based on the results of the BWS survey. We will stratify into two groups of 10 participants each:

1. Those participants who believe that “Living longer” is the most important attribute,

and

2. Those participants who believe another attribute is the most important attribute.

Staff will setup a time to interview eligible participants. Interviews will be scheduled within 14 days of the treatment decision (+ 14 days). A reminder email and/or phone call will be sent to participants the day before and the day of the interview. If participants do not respond during the pre-scheduled time, staff will reschedule the interview/reminders. Participants will be provided with a $25 gift card following completion of the interview.

Follow-up interviews will be around 3 months after the initial interview (+ 30 days). Interviews will follow the same format as the initial interview. Participants will be provided with a $25 gift card following completion of the interview.

Interviews will also be completed with up to 5 oncology clinicians and up to 5 palliative care clinicians. Clinicians will be referred to the study staff by the principal investigator. Interviews will take place over the course of 1 year and will not be time dependent upon patient enrollment. Participants will be provided with a $25 gift card following completion of the interview.

### 4.3.4 Participant Recruitment and Stratification

For the pilot testing, recruitment of patients will be stratified into the following 3 groups:

Aggressive lymphomas: 20 patients
Acute leukemias: 20 patients
Myeloma, Chronic lymphocytic leukemia (requiring treatment), chronic myeloid leukemia: 10 patients

We will target a population that exceeds the following diversity thresholds: 30% non-white race, 50% female, 25% rural.

For the qualitative interviews, recruitment of patients will be stratified into the following 2 groups:

1. Those participants who believe that "Living longer" is the most important attribute (n=10),

and

2. Those participants who believe another attribute is the most important attribute (n=10).

Recruitment of clinicians will be as follows:
Oncology clinicians (including physicians, advanced practice providers, nurse navigators): 2-5
Palliative Care clinicians (including physicians, advanced practice providers, nurse navigators): 2-5

### 4.3.5 The BWS survey

Priorities are how people value and rate the importance of multiple goals. In comparison, patient preferences reflect choices that patients make among several alternatives based on the expected benefit they get from each alternative. BWS surveys, a type of conjoint analysis, are one of several methods to measure

preferences. They are emerging as potentially important tools to elicit preferences of patients in the clinical setting.[20] BWS surveys involve asking participants a series of questions where they choose one attribute that is best and one attribute that is worst. In this survey, we will be asking patients to choose between the following 7 attributes:

a. Maintaining usual activities
b. Living longer
c. Avoiding becoming dependent upon others
d. Avoiding short-term side effects
e. Avoiding long-term side effects
f. Avoiding hospitalizations
g. Avoiding high out-of-pocket costs

We will be using a BWS survey that is adapted from a BWS survey we used to capture the preferences of patients with AML. Sampling 832 patients with the BWS survey, we illustrated that patients had the strongest concerns about treatment outcomes in psychosocial and physical domains.[32] Patients were most worried about dying from their disease, the long-term side effects of treatment, and becoming a burden to others.

### 4.3.6 **Longitudinal Assessments**

Participants will complete longitudinal assessments every 2 weeks (x 5). These assessments will include the BWS survey, CollaboRATE, WIWI, Decisional conflict scale, EQ-5D-5L, distress thermometer, and 7 items from the PRO-CTCAE. These assessments will begin after a treatment discussion with their oncology clinician.

The first longitudinal assessment will include a follow-up questionnaire that will assess patient acceptability and preliminary efficacy of the BWS to improve treatment decisions.

Participants will be given a $10 electronic gift card for each assessment.

### 4.3.7 **Extended Assessments**

After completing the longitudinal assessments (x6), participants will complete extended assessments every 3 months for the next 2 years (up to 7 assessments). These extended assessments will include the same questionnaires as the longitudinal assessments.

At 1 year on the study (the third extended assessment), participants will complete the 1 year questionnaire.

Participants will be given a $10 electronic gift card for each assessment.

### 4.3.8 Qualitative Interviews

Patients:
The qualitative interview will establish content validity of the BWS by cognitive interviews that will explore patients understanding of the content of the BWS. Specific domains to be covered will include:

- Cognitive interview to evaluate patient understanding of each of the questions asked within the BWS
- subjective value of potential outcomes including attributes elicited in BWS
- patient understanding of how preferences influenced treatment decisions including elicitation of important factors in the decision (if applicable),
- expected outcomes,
- additional attributes not included in the BWS, and
- preferences for potential interventions to improve preference elicitation and decision-making.

In addition to open ended questions as part of the interview, patients will complete a digit span test to test working memory and recall.

The follow-up qualitative interview will cover the same content as the first interview in addition to asking participants to reflect upon how their experience has changed over the time period between interviews.

Interviews with clinicians will explore barriers and facilitators of implementation of surveys to capture patient values and preferences. There is no follow-up interview with clinicians. Clinicians will not complete the Digit span test.

Interviews will be recorded to allow for qualitative analysis. Transcripts of the interviews will be made. The interviews should take about 30 minutes to complete. Following the interview a codebook will be created with emerging themes to allow for qualitative analysis similar to previous studies.[11]

### 4.3.9 Participant questionnaires

#### 4.3.9.1 Baseline Participant Questionnaire

Participants will complete a baseline questionnaire online via PRO Core upon enrollment. Questions related to the following domains will be asked of patients: race; ethnicity; household income; and insurance. This baseline questionnaire will

also include the PROMIS Cognitive Function 8a short form (8 items) to assess the perceived cognitive impairment of patients.

#### 4.3.9.2 Decisional conflict scale (DCS):

Decisional conflict will be evaluated with the validated survey measure decisional conflict scale.[31,33] Patients will complete the subscales of decision uncertainty (3 items) and perceived effective decision making (4 items).

#### 4.3.9.3 EQ-5D-5L:

Health-related quality of life will be evaluated with the validated survey measure EQ-5D-5L.[34] This is a 5 question survey.

#### 4.3.9.4 PRO-CTCAE:

Symptoms will be evaluated with the validated survey measure PRO-CTCAE.[35] Patients will complete the following 7 items: pain, fatigue, nausea, vomiting, constipation, diarrhea, appetite.

#### 4.3.9.5 PROMIS emotional distress short-form 8a

The PROMIS emotional distress short-form 8a is a 8 question survey developed to understand current emotional distress among patients and validated in numerous settings.

#### 4.3.9.6 Follow-up Questionnaire

Patient acceptability and preliminary efficacy (both defined above) will be assessed in this 2-item study-specific questionnaire.

#### 4.3.9.7 1 year Questionnaire

Patient acceptability and preliminary efficacy (both defined above) will be assessed in this study-specific questionnaire. Additionally, patients will be given open ended questions reflecting on how the BWS survey influenced the treatment decisions with their providers.

#### 4.3.9.8 CollaboRATE:

Preference clarity will be evaluated with the validated survey measure CollaboRATE.[30] This is a 3 question survey.

#### 4.3.9.9 WIWI

The “was it worth it” (WIWI) patient questionnaire is a subjective tool to assess a patient’s decisional regret related specifically to the chemotherapy decision.[38] We

will use two questions to avoid overlap with other questionnaires: Was it worthwhile for you to undergo chemotherapy? And If you had to do it over, would you undergo chemotherapy again?

#### 4.3.9.10 Decision Regret Scale (DRS):

Decisional regret will be evaluated with the validated survey measure DRS.[29] This is a 5-item questionnaire that has been validated as an important outcome measure of preference/value clarification measures.

#### 4.3.9.11 Digit Span Test:

The forward and backward assessments of the Digit Span test are subsets of the Wechsler Intelligence Scale, and when used separately, are considered validated measures of working memory.[39,40] Participants are assessed on their ability to repeat strings of numbers, increasing in length by one, until an error occurs on the reiteration of the string, or they reach a string length equal to 9. Participants will run through all forward strings before moving to the digit span backwards test, in which they will be asked to repeat strings of numbers in reverse order.

#### 4.3.9.12 Provider questionnaire

This survey will include 3 questions to capture treatment intent (curative vs. palliative), provider's assessment of which outcomes are most important to the patient, and outcomes most important to treatment decision making.

## 4.4 Expected Risks

### 4.4.1 Physical Risks

No physical risks are expected with this study.

### 4.4.2 Emotional Risks

Some questions in the patient questionnaires or interviews could create emotional distress or confusion. Patients will be instructed that the questionnaires are for research purposes only and any problem or symptom should also be reported to their physician or nurse.

### 4.4.3 Patient Confidentiality

We do not anticipate any breach of confidentiality. Any information about the participants obtained from this research will be kept as confidential as possible. All data obtained will be stored on a secure server.

## 4.5 Removal of Participants from Protocol

Participants will be removed from the protocol if they decide they no longer want to participate in the study.

# 5.0 TIME AND EVENTS TABLE

## 5.1 Time and Events Table

| | Study Enrollment | Interim | Longitudinal/ Extended assessments | Qualitative Interviews |
|---|---|---|---|---|
| **Screening** | X | | | |
| **Informed Consent** | X | | | |
| **HIPAA** | X | | | |
| **Enrollment Questions** | X | | | |
| **Decision Self-Efficacy** | X | | | |
| **Values subscale of DCS** | X | X (if not completed at enrollment) | X | |
| **BWS** | X | X (if not completed at enrollment) | X | X |
| **Baseline Questionnaire** | X | X (if not completed at enrollment) | | |
| **PROMIS cognitive function** | X | X (if not completed at enrollment) | | |
| **EQ-5D-5L** | X | X (if not completed at enrollment) | X | |
| **PRO-CTCAE** | X | X (if not completed at enrollment) | X | |
| **PROMIS emotional distress** | X | X (if not completed at enrollment) | X | |
| **Follow-up Questionnaire** | | | X (First timepoint only) | |
| **CollaboRATE** | | | X | |
| **WIWI** | | | X | |
| **DRS** | | | X | |
| **1 year Questionnaire** | | | X (3rd extended assessment) | |
| **Qualitative interview** | | | | X |
| **Digit Span Test** | | | | X (Patients only) |

| **Provider assessment** | |
|---|---|
| | **Study Enrollment** |
| **Screening** | X |
| **Informed Consent** | X |
| **HIPAA** | X |
| **Provider Questionnaire** | X |

# 6.0 UNANTICIPATED PROBLEMS

## 6.1 Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects or others (UPIRSO) refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

### 6.2 Reporting

Any UPIRSO that occurs during the conduct of this study and that meets all three criteria listed in 6.1 must be reported to the UNC IRB using the IRB's web-based reporting system. The PI will also report any UPIRSO to the PCRC and the NINR. The PI will be responsible for assessing developments in the literature and results of related studies by conducting a literature review once during the grant period to identify relevant information that may impact the safety of participants or on the ethics for the research study.

## 7.0 STATISTICAL CONSIDERATIONS

### 7.1 Study Design

This is a mixed methods pilot study designed to evaluate the content validity of the BWS survey.

### 7.2 Sample Size and Accrual

Our primary objective is to establish content validity of the BWS survey. Based on established guidelines, 7-10 participants are needed to establish content validity of survey items in cognitive interviews.[41–43] As we will be stratifying patients for cognitive interviews into 2 groups, we will have 10 participants per stratification to ensure saturation in both.

Based on our prior data, we anticipate that we will have a 3:1 split between patients who value living longer most and those who value another attribute most. Therefore, we will need to recruit at least 40 patients to have 10 patients who value another attribute most to participate in cognitive interviews. Accounting for variability and drop out, we will plan to recruit 50 patients total to be able to recruit 10 patients in this group.

10 clinicians will provide for saturation for qualitative interviews.

This study was not designed to be powered to evaluate secondary endpoints or exploratory endpoints.

We expect to accrue up to 50 patients over the time of the study. We see over 500 new patients with hematologic malignancies per year within the division of hematology.

## 7.3 Data Analysis Plans

### 7.3.1 Primary Aim: Content Validity

The primary aim of this study is to evaluate the content validity of the BWS survey. This will be established by mixed methods. We will conduct cognitive interviews with patients in accordance with FDA guidance on patient-reported outcomes measurement development to evaluate patient understanding of each concept within the BWS and explore other areas that were important but were not included in the survey.[41] We will produce a cognitive interview summary based on published guidance to determine content validity from the interviews.[41] Additional interview questions from the qualitative interview will be used to establish the importance of individual attributes to patients using interpretive phenomenological analysis (IPA)[44] and provide additional support to BWS content validity. Results from the ranking exercise (embedded within the BWS survey) will also be reported. To integrate data from each source, we will follow a sequential explanatory approach: we will produce narrative summaries of each aspect of the critical determinants identified in interviews followed by a summary of both quantitative and qualitative data. Together, these data will provide convergent support of the content validity of the BWS survey.

### 7.3.2 Secondary Aims

Patient acceptability:

We will conclude the BWS is acceptable if $\geq$70% of patients (35/50) report that it is acceptable. Hypothesizing 80%, the exact binomial 95% CI will be 66.3-90.0%.

Preliminary efficacy:

We will conclude the tool is potentially efficacious if efficacy **(**defined as participants answering "moderately effective/very effective" to the question: "How effective was the survey to help you and your doctor choose a treatment that was consistent with your goals?") is reached in >50% of patients. Estimating 5-7% missing data from enrollment to initial longitudinal questionnaire (from other PRO assessments in advanced cancer patients[45,46]) and hypothesizing a rate of 75%, the exact binomial 95% CI will be 60.0-86.6%.

Preliminary completion rates:

Frequencies will be reported at each time point. Completion rate out of the original 50 participants will be reported at each month with exact binomial 95% CIs with reasonable precision, no wider than ±14.5%. Reasons for dropout will be summarized as available. Associations of baseline patient characteristics with completion rates will be explored using Wilcoxon Rank sum and Kruskal-Wallis tests.

### 7.3.3 **Exploratory Aims**

Repeated measures analyses, using generalized linear mixed models, will be used to describe change in preferences over time and the relationship to clinical characteristics with a particular focus on evaluating the influence of response (e.g. remission) on preferences. Performance of the BWS survey will be evaluated including convergent validity, within-set dominated pairs, and attribute dominance.[21,47] We will use frequency analysis to describe the strength of aggregate preferences for outcomes, and differences by age, race, gender, and clinical response.[19] We will perform exploratory, hypothesis-generating analyses to compare within-person changes in preferences across timepoints, the relative stability of betas for attributes over time, and explore associations between preferences, decisional outcomes[8,29–31], patient-reported symptoms,[35] health-related quality of life[34], and provider perceptions. These analyses are exploratory as our sample size is relatively small. These exploratory analyses will inform future studies.

## 7.4 Data Management/Audit

Data will be stored on a shared, Oracle-Based framework which provides a highly secure IT environment, utilizing a secure authentication mechanism, the Transport Layer Security (TLS) system. This security mechanism supports encryption in both directions (to and from the website) across all devices including mobile devices such as smartphones. Backup files of all data will be included on this server. Only those trained to work with sensitive data will have access to the server. This project will have a specific folder on the server that will require password access for all users.

Data collection will be done by the study team. Study personnel will input data from patient interview or chart review into the database.

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC). Data sources included in this study will include data from medical records, questionnaires, and audio recordings. Data will be extracted from medical records by trained clinical research assistants and placed in a study-specific database per the protocol. Questionnaires will be delivered electronically. Data will be automatically transferred to the database. Audio recordings will be produced during the qualitative interviews and will be transcribed by trained personnel. The transcripts will be transferred electronically into the secure database. Data will undergo periodic review by the PI and the project manager for integrity.

Meetings/teleconferences will be held at a frequency dependent on study accrual. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

Once complete, data will be de-identified and transferred to the Palliative Care Research Consortium (PCRC) repository for dissemination.

# 8.0 STUDY MANAGEMENT

## 8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment into this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

## 8.2 Required Documentation

Before the study can be initiated, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

## 8.3 Registration Procedures

Patient enrollment will be tracked in a secure database as outlined above.

## 8.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

### 8.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

### 8.4.2 Single Patient/Subject Exceptions

We will not allow single patient exceptions in the study. Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

### 8.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

**Protocol Deviations:** UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

**Protocol Violations:** Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report UPIRSO.

**Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO):** Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 6.1) must be reported by the Study Coordinator using the IRB's web-based reporting system. The PI will be responsible for reporting UPIRSO to the PCRC and the NINR.

## 8.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

## 8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

## 8.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

## 8.8 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the UNC Lineberger Data and Safety Monitoring Committee (DSMC).

**Monitoring Procedures:**
Meetings/teleconferences will be held at a frequency dependent on study accrual. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study once the protocol is finalized. Based on the "minimal risk" nature of the study (behavioral, non-therapeutic trial), it is anticipated that the DSMC will review the study on an annual basis. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB. Summaries will also be made available for review by the PCRC and the National Institute of Nursing Research (NINR). The PI will be responsible for submitting summaries to the PCRC and the NINR. In accordance with our institutional guidelines, studies deemed "minimal risk" will not be audited.

**Minimization of Risk:**
Some questions in the patient questionnaires, interviews or survey could create emotional distress or confusion. Patients will be instructed that the questionnaires are for research purposes only and any problem or symptom should also be reported to their physician or nurse.

We do not anticipate any breach of confidentiality although recognize that a breach in confidentiality may result in psychological, social, or economic harm to a patient if the details of the medical record become available to others. Any information about the participants obtained from this research will be kept as confidential as possible. All data obtained will be stored on a secure server.

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## 10.0 APPENDICES

Included appendices:

1. Baseline questionnaire
2. PROMIS cognitive function
3. BWS survey
4. Decision Self-Efficacy Scale
5. DCS
6. EQ-5D-5L
7. PRO-CTCAE
8. PROMIS emotional distress SF 8a
9. Follow-up questionnaire
10. CollaboRATE
11. DRS

12. 1 year questionnaire
13. Decision Self-efficacy
14. Qualitative interview guide, initial, patients
15. Qualitative interview guide, follow-up, patients
16. Qualitative interview guide, clinicians
17. Digit span test
18. WIWI
19. Provider questionnaire