IRB Research Proposal

Title: Removing Transfusion Dependence as a Barrier to Hospice Enrollment
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IRB #: 1542176

Clinicaltrials.gov: NCT05063591

Specific Aims:

1. To gather data on the feasibility of providing transfusions to patients with hematologic malignancies enrolled in hospice.

Hypothesis 1: Providing palliative blood transfusions to patients with hematologic malignancies enrolled on hospice will be feasible with respect to cost, patient interest, and safety.

2. To measure the time enrolled on hospice in our study population and compare them to historical controls.

Hypothesis 2: : Removing transfusion dependence as a barrier to hospice enrollment for patients with hematologic malignancies will results in increased length of time on hospice when compared to historical controls

3. To measure End of Life (EOL) care quality outcomes (as a surrogate for meaningful hospice use) in our study population and compare them with historical controls.

Hypothesis 3: Removing transfusion dependence as a barrier to hospice enrollment for patients with hematologic malignancies will result in improved EOL care quality outcomes in this population, as measured by the following: number of days enrolled on hospice, number of days in the ICU in the last 30 days of life, death in an acute care hospital, chemotherapy in the last 14 days of life, Medicare spending in the last 30 days of life, and number of inpatient days in the last thirty days of life.

4. To measure quality of life for caregivers of patients in our study population, and caregiver perception of EOL quality care for patients with hematologic malignancies.

Hypothesis 4: Removing transfusion dependence as a barrier to hospice enrollment for patients with hematologic malignancies will improve caregiver QOL as patients transition to hospice, and timely hospice enrollment will result in caregiver perception that end of life care was of adequate quality.

Significance/Background:

The benefits of hospice care at the EOL are well established in patients with solid organ malignancies. Hospice care at EOL in these patients has been shown to improve quality of life for both patients and families, as well as family perceptions of quality EOL care.[1, 2] Timely referral to hospice and avoidance of aggressive care at the EOL are set forth as quality standards by the American Society of Clinical Oncology (ASCO) and the

National Quality Forum (NQF).[3, 4] Key care quality measures as delineated by the NQF in 2016 include: 1) avoidance of intensive care unit (ICU) admission in the last 30 days of life, 2) avoidance of chemotherapy administration in the last 14 days of life, and 3) avoidance of death in an acute care hospital, which is a preference expressed by a majority of people with cancer and their families

Patients with hematologic malignancies (HM) have been demonstrated to have inferior EOL care quality outcomes. While hospice care at the EOL is known to provide the highest care quality during this time, patients with HM enroll on hospice later and at lower rates than patients with solid tumors. As a result, they receive more aggressive EOL care, with more days in the hospital at the EOL, higher rates of chemotherapy at the EOL, and more days in the ICU. [5-8] While the reasons for this are myriad, one major barrier to timely hospice enrollment for these patients is transfusion dependence. [7] The structure of Medicare hospice benefit, while not explicitly forbidding of blood transfusions, makes coverage for transfusions financially unfeasible for hospice agencies. Many patients with HM are transfusion dependent at the EOL and are loathe to forgo transfusions even after cancer-directed therapy has been exhausted, as they perceive symptomatic relief attributable to transfusions. The American Society for Hematology has recently released a policy statement urging the Center for Medicare and Medicaid Services to address this issue and has called for exploration of ways to improve access to transfusions for hospice patients. [9]

The overall objective of this pilot project is, through external funding of blood transfusions, to demonstrate that it is feasible to provide palliative blood transfusions for these patients while enrolled on hospice. The central hypothesis is that providing access to blood transfusions will result in timely referral to hospice and avoidance of aggressive care at the EOL. While direct quality of life measurements as they relate to blood transfusions will not be obtained, earlier time to hospice enrollment, and longer time enrolled, will improve EOL care quality outcomes and allow for more meaningful hospice use.

The results of this pilot study will provide evidence of feasible translation of the novel approach to improving EOL care quality to clinical practice. We will use this experience: 1) to secure funding for a larger study with a power to demonstrate improved EOL care quality outcomes in this setting and 2) as data to support groundbreaking policy changes regarding transfusion availability for hospice enrollees that could significantly impact EOL care quality outcomes in this patient population.

Progress Report/Preliminary Studies:

We have previously conducted two studies that allowed for hypothesis generation in this pilot and provide solid preliminary data. First, we conducted a population-based analysis of Medicare beneficiaries with leukemia which demonstrated that transfusion dependent patients have a 51% shorter hospice length of stay than their non-transfusion dependent counterparts, suggesting that transfusion dependence was an independent barrier to hospice enrollment. Transfusion-dependent patients had also worse other indicators of

EOL care quality, as well as higher Medicare spending in the last 30 days of life; hospice enrollment was associated with better indicators of EOL care quality and lower costs. [7]

Second, we performed a population-based analysis of EOL care quality outcomes among Medicare beneficiaries with various hematologic malignancies. We described outcomes that were inferior to those reported in solid tumor malignancies. Beneficiaries with hematologic malignancies had lower rates of hospice enrollment, were more likely to die inpatient, and more likely to have an ICU admission in the last 30 days of life than in a study by Teno, et al. examining the same outcomes in a contemporary population of beneficiaries with all types of cancer. [10,11]

Experimental Design and Methods:

Study Design and Schema

We propose to conduct a single-center, prospective pilot study to demonstrate the feasibility of providing blood transfusions to patients with HM enrolled on hospice, and to evaluate both EOL care quality outcomes in these patients, and caregiver quality of life and perception of patient EOL care quality. Patients with aggressive hematologic malignancies who are transfusion dependent and not pursuing further cancer directed therapy will be recruited at the Lifespan Cancer Center.

Study Methods

Patient Eligibility Criteria

Inclusion Criteria will include patients with all the following characteristics:

A) Aged 18 and older
B) Advanced hematologic malignancies
C) Hospice eligible as determined by their primary hematologist
D) Have opted to forego further cancer-directed therapy.
E) Transfusion Dependent: Requiring at least 2 units of blood products (red blood cells or platelets, in the previous 1 month)

Exclusion Criteria will include either of the following criteria:

A) Patients with major psychiatric illness
B) Patients without the ability to speak and read English

Caregiver Eligibility Criteria

Inclusion Criteria will include caregivers with all the following characteristics:

A) Aged 18 and older
B) Be identified by the patient as the primary caregiver

Exclusion Criteria will include either of the following criteria:

A) Caregivers with major psychiatric illness

B) Caregivers without the ability to speak and read English

Patient Screening, Recruitment, and Enrollment Procedures
Prior to the start of the study, the PI will meet with all members of the Malignant Hematology team, including MDs and Advanced Practice Providers (APPs) to review screening, recruitment, and enrollment procedures. All MDs and APPs in the malignant hematology department will be included as sub-investigators with the ability to enroll patients. The PI will request that clinicians who identify patients that are hospice-eligible will reach out to the research team for potential trial enrollment. The PI or research assistant will also speak weekly with the malignant hematology team to screen for patients who may be eligible for enrollment.

Once a patient is determined to be potentially eligible, the primary clinician for the patient will be tasked with the initial discussion regarding interest in trial participation as part of the discussion regarding transition to hospice. If the patient expresses interest in the trial the primary physician will then reach out to the PI or research assistant to notify them. The research assistant, and/or the primary hematologist or APP will then meet with the patient to review the trial and review and sign the consent.

Patients will also be asked to identify their primary caregiver. The caregiver will also meet with the research assistant and /or the primary hematologist or APP to discuss enrollment and review and sign consent for the caregiver assessment portion of the study. If a patient does not identify a primary caregiver or if the patient's caregiver is not interested in participating in their portion of the study this will not affect the patient's ability to enroll.

Main Study Intervention:
Once enrolled, patients will be given the option of having either a weekly clinic visit or weekly telephone call to assess their symptom burden. Patients will be evaluated by the research assistant and/or the primary hematologist or APP either in clinic or over the phone to see if they are having fatigue or breathlessness that they feel would benefit from RBC transfusion, or if they have any bleeding or petechiae consistent with symptomatic thrombocytopenia. A telephone script will be provided for patient evaluation. If they report these symptoms, they will be scheduled for an infusion visit, at which point a complete blood count (CBC) will be checked, as ordered by their primary hematologist or advanced practice provider. If the CBC demonstrates a hemoglobin or a platelet count low enough to be causing the patient's symptoms and therefore warranting a palliative transfusion, then RBC and/or platelet transfusion will be administered in the clinic, as determined by their primary hematologist or APP, during the same visit.

The blood transfusion and any associated labs or medications, including pre or post medications for the prevention or treatment of transfusion reactions, will be paid for by the study. At the time of enrollment patients will be notified of the possibility of having a transfusion reaction severe enough that would require hospitalization for management. Patients will be notified that if they chose to proceed with hospitalization they will be

required to revoke hospice and be removed from the study. They will be able to enroll in hospice again after discharge from the hospital.

Caregiver Quality of Life Measurements:
Caregivers will have a Caregiver Quality of Life –Cancer (CQOLC) survey administered to them by the research assistant at the time of enrollment, and then weekly thereafter. They will be contacted by the research assistant or PI separate from the patient encounters and telephone visits.

Caregiver Assessment of Patient End of Life Care Quality:
One week after enrollment, a Caregiver Evaluation of Quality of End-of-Life Care (CEQUEL) will be administered to the caregiver either by phone (if the patient does not elect to come in for transfusion), or at the infusion visit. One month after the patient death, the caregiver will be contacted by phone and a subsequent CEQUEL questionnaire will be administered.

Data Collection and Data Analysis

1. **Primary outcome measure: Feasibility of the Care Model**
As a measure of patient interest in continuing transfusions once hospice-ready, we will track the number of patients approached and measure the percentage who elect to enter the study versus those who enroll on hospice through the traditional channel and forego further transfusions. As a measure of palliative transfusion needs, we will track the number of clinic/infusion visits, the number of transfusions provided per patient, and the indication for transfusions provided. We will also track cost of transfusions and care provided that is associated with this treatment.

2. **Secondary outcome measure: Time enrolled on hospice.**
As a measure of benefit we will track the time enrolled on hospice of patients enrolling in the study. We will compare these data to: 1) a historical cohort at our institution, 2) population-based data we obtained through our previous SEER-Medicare linked database analysis.

3.**Secondary outcome measure: End-of-Life Care Quality Measures**
We will collect data associated with established EOL care quality measures as delineated by the NQF, including: number of days on hospice, inpatient days in the last thirty days of life, ICU days in the last thirty days of life, inpatient deaths, and use of chemotherapy within fourteen days of death. We will compare these data to: 1) a historical cohort at our institution, 2) population-based data we obtained through our previous SEER-Medicare linked database analysis.

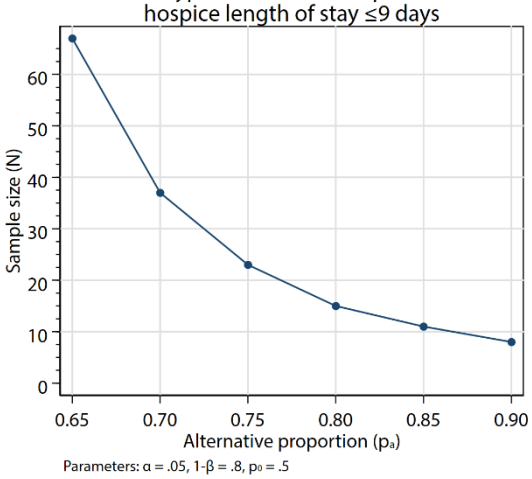
4. **Exploratory outcome measure: Caregiver Quality of Life and Caregiver Assessment of End-of-Life Care Quality**
We will collect CQOLC data as described above and compare scores at onset of trial enrollment to scores obtained longitudinally over the course of the trial to assess for any

impact of trial enrollment on caregiver quality of life, as well as measure caregiver perception of end of life care quality as a descriptive outcome.

4. **Statistical Plan**

The main objective of this pilot study will be to demonstrate feasibility of the proposed novel care model for end-of-life for patients with blood cancers. For **Specific Aim 1**, we define feasibility as: 1) 50% acceptance rate of the participation among screened subjects, 2) no more that 10% rate of disenrollment from the study to receive medical care for complications of transfusions or to resume their prior care model, and 3) net balance of observed transfusion-related costs with reimbursement to the hospice organization. These considerations are based on expected accrual and acceptable drop-out rate for a future larger study. Prior research indicates that 58% of Medicare beneficiaries enroll in hospice before death, compared with 67% of decedents with solid tumors, median duration of hospice length of stay is 9 versus 14 days, respectively, and the proportion of patients spending ≤3 days on hospice before death is 24% and 19%, respectively. [12] (Egan et al., 2020). Therefore, in **Specific Aim 2**, we will consider a meaningful observation in this pilot study if at least 7 of 10 participants will be enrolled in hospice for >9 days before death. This pilot study is not intended to generate sufficient data for statistical testing of hypotheses. However, observing 7 out of 10 participants with hospice length of stay of >9 days would provide preliminary data for design of a future, adequately powered trial, namely power of 80% with one-sided type 1 error rate of 0.05 to reject the null hypothesis (of 50% of patients with hospice length of stay equal to 9 days) in a future study with *N*=37 (See Figure). Additional EOL care quality measures will be described and placed in context (without statistical testing) of population-based outcomes defined in our prior research: number of inpatient days spent within the last 30 days of life (median 4 in Medicare data), proportion of patients dying in the acute care hospital (32%), proportion of patients admitted into ICU in the last 30 days of life (39%), proportion of patients receiving chemotherapy within the last 14 days of life (13%).

Figure. Sample size needed to reject the null hypothesis of 50% of patients with hospice length of stay ≤9 days



In **Specific Aim 3**, we will describe the patient caregivers' quality of life using the CQOLC instrument, which in a recent study of caregivers for older (age ≥65) patients with cancer showed a mean score of 84.6 ± 23.5. [13] A study with N=10 has a power of 80% with one-sided type 1 error rate of 0.05 to detect a change in the score with effect size equal to 1 standard deviation (SD), therefore this effect size will be considered promising for the future larger study.

Accrual: 10 patients.

Benefits:

The potential benefits to the patient population under investigation are that removing transfusion dependence as a barrier to hospice enrollment will shorten time to hospice enrollment, will result in improved EOL care quality outcomes, will improve caregiver QOL, and will result in caregiver perception that end of life care was of adequate quality.

The potential benefit to society will be that it will provide evidence of feasible translation of the novel approach to improving EOL care quality to clinical practice. It will allow us to use this experience: 1) to secure funding for a larger study with a power to demonstrate improved EOL care quality outcomes in this setting and 2) as data to support groundbreaking policy changes regarding transfusion availability for hospice enrollees that could significantly impact EOL care quality outcomes in this patient population.

Risks:

Risks associated with enrollment are those associated with the risks of blood transfusions. These are:

- Severe Allergic Reaction
- Respiratory distress due to fluid overload (Transfusion-Associated Circulatory Overload), or
- injury to the lungs (Transfusion-Related Acute Lung Injury
- Bacterial contamination
- Fever, chills, rash
- Hemolytic transfusion reaction (an immune reaction where antibodies lead to destruction of
- transfused red blood cells)
- Mistransfusion (human error leading to the transfusion of the wrong product)

The most common reactions are mild allergic or febrile reactions, and are not life-threatening. Severe transfusion reactions, such as those causing respiratory distress, may be life threatening.

Risks also include breech of privacy, but data will be stripped of PHI before publication, will be digitally stored on the Lifespan intranet in a password-protected file and any hard copy will be physically stored in a locked drawer in a locked room in the PI's office.

Safety:

The Brown University Oncology Research Group (BrUOG) Data Safety Monitoring Board (DSMB) will review the outcome data and cumulative toxicity data from this trial during their meetings, two times per year (typically May and November) with any additional meetings scheduled when needed. Lifespan has agreed to provide the data to BrUOG for the DSMB reviews.

The responsibilities are as follows:

- The BrUOG DSMB review will be coordinated by BrUOG after data and toxicities on this trial are provided to BrUOG prior to the meeting for review.
- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).

Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial

Confidentiality of data:

The data collected will be stripped of any identifiable information before publication. Data will be stored on the Lifespan intranet in a password-protected file. Physical copies of data will be stored in a locked drawer in the PI's locked office. Finalized results will be published in a group format.

References

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8) Sexauer, A., et al., Patterns of hospice use in patients dying from hematologic malignancies. J Palliat Med, 2014. 17(2): p. 195-9
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11) P.C. Egan, LeBlanc, T.W., and A.J. Olszewski, End-of-Life Care Quality Outcomes Among Medicare Beneficiaries with Hematologic Malignancies. *Blood* (2018) 132 (Supplement 1): 829
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