Title:	**Home or Away From Home: Comparing patient and caregiver reported quality of life and other patient-centered outcomes for inpatient versus outpatient management of neutropenia in children with AML or MDS receiving standard intensive AML frontline chemotherapy**
Short Title:	Aim 3: AML/MDS Neutropenia Quality of Life
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TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATIONS

ALSF	Alex's Lemonade Stand Foundation
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
CHOP	The Children's Hospital of Philadelphia
CI	Confidence Intervals
COG	Children's Oncology Group
FAC	Family Advisory Council
HRQOL	Health-related quality of life
ICU	Intensive Care Unit
MDS	Myelodysplastic syndrome
PAC	Patient Advocacy Committee
PCO	Patient-Centered Outcomes
PCORI	Patient-Centered Outcome Research Institute
PedsQL™	Pediatric Quality of Life measurement modules
REDCap™	Research Electronic Data Capture
SD	Standard Deviation

DEFINITIONS

Bacteremia	Positive blood culture for a bacterial pathogen unless the bacterium is an organism considered a common commensal organism by the National Healthcare Safety Network
Early Discharge	Discharge to outpatient management during neutropenia within 3 days after chemotherapy completion in a given course
Neutropenia	Absolute Neutrophil Count <200/μL
Caregiver	A parent or adult that is the legal guardian of the pediatric study participant

ABSTRACT

Context: (Background)

Treatment for pediatric acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) involves intensive chemotherapy regimens that result in periods of profound neutropenia leaving patients susceptible to severe infectious complications. Infectious complications are the leading cause of treatment related mortality among AML and MDS patients, but there are little clinical data to inform whether management of neutropenia post AML chemotherapy should occur in an outpatient or inpatient setting. Further, no studies have been conducted that assess the impact of neutropenia management strategy on the quality of life of pediatric patients with AML/MDS and their caregivers.

Objectives:

The primary objective of this study is to compare patient and caregiver quality of life and other patient-centered outcomes (PCO) for inpatient versus outpatient management of neutropenia in children with AML or MDS receiving standard intensive AML frontline chemotherapy.

Study Design:

This is a prospective observational cohort study.

Setting/Participants:

Participants will be patients less than 19 years of age at their initial AML or MDS diagnosis (and their caregivers) receiving or having received frontline AML chemotherapy from fifteen participating pediatric hospitals across the United States (US). Due to the nature of the survey collected data, only dyads who are English/Spanish literate will be eligible. We expect to identify 139 patient-caregiver dyads, of which we anticipate that approximately 118 will consent to participate over the study period to compare patient- and caregiver-identified outcomes of neutropenia management in the outpatient and inpatient settings.

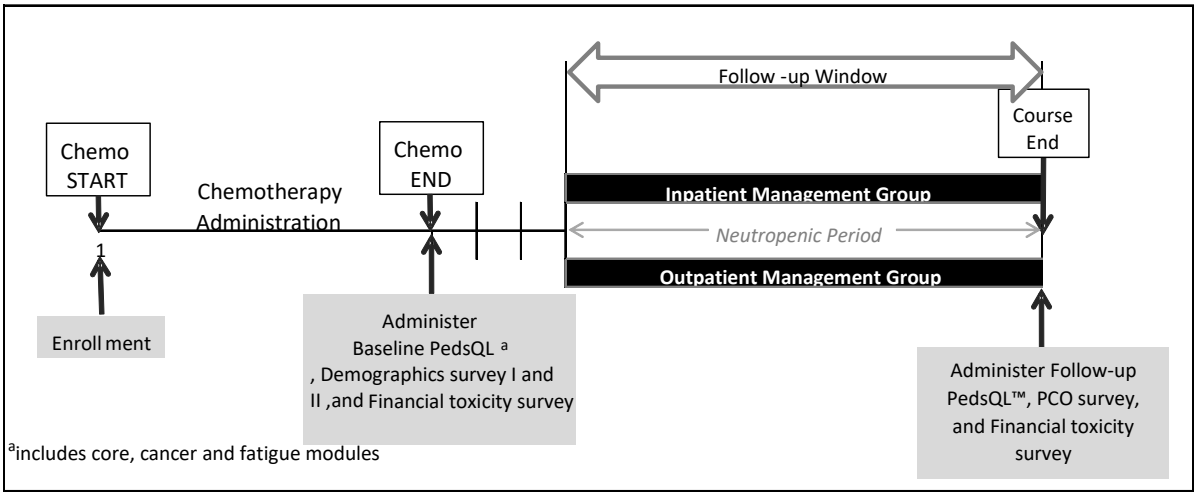
Study Interventions and Measures:

There is no study intervention. Main outcomes include scores on health-related quality of life surveys, as well as additional patient- and caregiver- identified outcomes.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Study Visits**	
Visit Number		**1**	**2**
Informed Consent/Assent	X		
Review inclusion/exclusion criteria	X		
Baseline PedsQL™		X	
Demographic survey		X	
Demographic survey II		X	
Follow-up PedsQL™			X
PCO survey			X
Financial toxicity survey		X	X

FIGURE 1: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Acute myeloid leukemia (AML) is the second most common pediatric hematologic malignancy with approximately 600 new cases per year among patients under 20 years of age. Although AML accounts for only about 20% of leukemias in children, it is responsible for more than half of pediatric leukemia deaths (1). The prognosis of children with AML has improved greatly over the past 30 years (2, 3, 4), attributable largely to the intensification and standardization of chemotherapy regimens.

All pediatric patients with newly diagnosed AML receive multiple consecutive courses of intensive myelosuppressive chemotherapy aimed to attain complete remission (induction) and to prevent relapse (intensification) (5). Each regimen is followed by a period of prolonged severe neutropenia during which patients are at high risk for infection and hemorrhage. Previous reports have found that 57-80% of febrile neutropenia episodes among pediatric AML patients are compromised by at least one microbiologically documented infection (6, 7) with bacteremia constituting the most prevalent infection (8). These infectious complications remain a major cause of therapy-associated morbidity and mortality in children with AML (9, 10).

Recently published pediatric neutropenia guidelines make no specific recommendations regarding discharge from hospital after chemotherapy for AML because "there are no validated schemas for defining those patients at high-risk of developing complications of fever and neutropenia" (11). As a result, clinicians are left to decide whether to keep a child in the hospital until the neutropenia resolves (on average 35 days) or discharge a child to outpatient management within a few days of chemotherapy completion with instructions to return if symptoms of infection develop. Physicians that elect to observe patients with neutropenia in the hospital do so under the assumption that hospital observation will reduce the risk of serious infection and thereby reduce delays in starting the next course of chemotherapy. Furthermore, this approach assumes that the potential reduction in infection outweighs the potential negative consequences of a prolonged inpatient stay—namely reduced quality of life, increased exposure to multi-resistant nosocomial infections, and increased healthcare cost. There is documented variation in practice across Children's Oncology Group (COG) institutions on inpatient versus outpatient management of neutropenia with approximately 60% of COG institutions reporting a policy to always keep patients hospitalized during severely neutropenic periods and the remaining 40% of hospitals reporting a policy of home management some or all of the time (12, 13). This variation in practice highlights the need for additional data on clinician-centered and patient-centered outcomes to appropriately guide the management of neutropenia in pediatric AML patients.

Myelodysplastic syndromes (MDSs) are a rare heterogenous group of hemopoietic clonal disorders characterized by ineffective hemopoiesis and frequent evolution to leukemia. Children with clinical and morphological features of MDS but with the cytogenetic features typical of AML are often treated with same intensive frontline chemotherapy used to treat AML. (38) Thus, questions regarding clinician-centered and patient-centered outcomes in

relation to outpatient versus inpatient management of neutropenia would apply equally to such patients.

1.2 Relevant Literature and Data

The limited literature on the clinical consequences of outpatient versus inpatient management of neutropenia in AML is focused on the experience of adult patients. Adult patients discharged early to outpatient supportive care consistently had shorter cumulative lengths of stay than inpatients (14-21). Additionally, early discharge of adult AML patients receiving chemotherapy has been associated with fewer and shorter febrile episodes (18, 22), a better response to first line antibiotics, and shorter duration of intravenous antibiotic administration (16, 18, 21, 22). While these adult studies provide some reassurance that outpatient management may be safe and feasible they are limited as most included data from only a single institution, had very small sample sizes, or lacked an appropriate inpatient reference population. Furthermore, it is not appropriate to extrapolate these adult findings to pediatric patients as the risk profile for children may be much different.

The published literature with respect to outpatient management of neutropenia in pediatric AML is limited to a single study of only 13 patients from one hospital, which found similar rates of relapse and mortality for outpatient versus inpatient management of neutropenia (23). In our own preliminary analyses based on administrative resource utilization data from 43 free-standing children's hospitals in the US, we found that patients who were discharged early to outpatient management following AML induction and intensification chemotherapy courses incurred fewer cumulative days of hospitalization, but were frequently readmitted and had higher rates of antibiotic, vasopressor, and supplemental oxygen utilization than patients who remained inpatient during the entirety of their neutropenia. In the absence of clinical data and laboratory confirmation, it is unclear whether these observed increases in resource utilization are an accurate proxy for a greater incidence of infection or more severe infection in the early discharge patients.

Decisions regarding supportive care strategies are intended not only to improve clinical outcomes but also to impact patient quality of life outcomes, such as minimizing the psychological, social and spiritual challenges related to therapy (24). Thus, it is imperative to determine the impact of a chosen neutropenia management strategy on the child's quality of life and interactions with his or her broader social environment, including impact on the family. There is a dearth of literature on child and caregiver (parent/guardian) perspectives on outpatient versus inpatient management of neutropenia (25, 26) or the impact of neutropenia management strategy on quality of life (27) in pediatric cancer patients. The one qualitative study on parent preferences for neutropenia management in pediatric cancer found that most respondents preferred hospital-based treatment once a patient had developed a fever during neutropenia (25). Factors that influenced parent preference for febrile neutropenia management included convenience and disruptiveness to family life, concerns about the child's physical health (including infection), and concerns about the child's emotional wellbeing. While this study was a good first step in identifying PCO for febrile neutropenia management in pediatric cancer it has some notable limitations: it was conducted at one center in Canada, it only included parent perspectives on febrile

neutropenia management and not management of neutropenia prior to fever onset, children were not interviewed, and it involved the elicitation of parent preferences via hypothetical scenarios versus more in-depth study of the actual experience of neutropenia management in the hospital or the home.

There are no studies evaluating clinician-centered and patient-centered outcomes in relation to outpatient versus inpatient management of neutropenia among MDS patients treated with standard intensive AML frontline chemotherapy. However, these patients suffer the same severe prolonged neutropenia as similarly treated AML patients and as such, assessments of patient quality of life and other family-centered outcomes for outpatient versus inpatient management of neutropenia would be equally informative to decisions on their supportive care strategies.

In order to appropriately inform the decision for outpatient versus inpatient management of neutropenia associated with pediatric AML chemotherapy, a comprehensive study that considers pertinent clinical, patient and caregiver centered outcomes is necessary. Given that infectious complications are the leading cause of treatment-related mortality among AML patients (28) and among MDS patients (39, 40), identifying such a neutropenia management strategy that leads to the best clinician and patient/caregiver identified outcomes will have a substantial impact on care of these patients.

1.3 Compliance Statement

This study will be conducted in full accordance with all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46. All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of this study is to establish important comparative effectiveness data on patient-directed outcomes for outpatient versus inpatient management of AML neutropenia or MDS in individuals receiving standard AML frontline chemotherapy.

2.1 Objectives

The primary objective of this study is to compare patient and caregiver reported quality of life and other PCO (established through previous qualitative interviews conducted by a medical sociologist at CHOP) for inpatient versus outpatient management of neutropenia in children with AML or MDS receiving standard intensive AML frontline chemotherapy.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This prospective observational cohort study will evaluate patient- and caregiver-directed outcomes of inpatient versus outpatient management of neutropenia following chemotherapy in children with AML or MDS.

3.2 Study Duration, Enrollment and Number of Sites

This study plans to include patients and their caregivers who are undergoing frontline chemotherapy starting June 1, 2016 or after.

3.3 Total Number of Study Sites/Total Number of Subjects Projected

3.3.1 Duration of Study Participation

Eligible patients will be approached for consent at any time from initial AML or MDS diagnosis through the last day of chemotherapy in the frontline treatment course under study. The maximum duration of enrollment is from the initiation of their current chemotherapy course until the last day of their subsequent chemotherapy course. This duration is estimated to be approximately 30-40 days.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

Surveys will be administered at the following fifteen US investigative sites: Children's Hospital of Philadelphia (*Philadelphia, PA*), Children's Healthcare of Atlanta (*Atlanta, GA*), C.S. Mott Children's Hospital (*Ann Arbor, MI*), Ann & Robert H Lurie Children's Hospital of Chicago (*Chicago, IL*), Arkansas Children's Hospital (*Little Rock, AR*), Children's Medical Center of Dallas (*Dallas, TX*), Texas Children's Hospital (*Houston, TX*), Primary Children's Medical Center (*Salt Lake City, UT*), Children's Hospital of Michigan (*Detroit, MI*), Lucile Packard Children's Hospital Stanford (*Palo Alto, CA*), St. Jude Children's Research Hospital (*Memphis, TN*), Seattle Children's Hospital (*Seattle, WA*), Children's Hospital Colorado (*Denver*), Nemours/A.I. duPont Hospital for Children, and DFCI/Boston Children's Hospital (*Boston, MA*). These sites were chosen based on geographic location, their substantial AML/MDS patient volume, and the variation in primary strategy of neutropenia management.

We expect approximately 278 subjects across all sites to be enrolled and approximately 236 subjects to be evaluable (118 patients and 118 caregivers).

3.4 Study Population

The study population will include all AML and MDS patients who are receiving a planned frontline chemotherapy course at any of the fifteen pediatric institutions across the US starting June 1, 2016. Patients discharged within 3 days after chemotherapy completion will be categorized as 'early discharge' to outpatient management during neutropenia. Patients remaining in the hospital more than 3 days after chemotherapy completion will be categorized as inpatient management.

Caregivers of these patients will also be included.

3.4.1 Enrollment Criteria

3.4.1.1 Inclusion Criteria

1) Participants will be enrolled as patient-caregiver dyads. The patient must be:

   - Less than 19 years of age at initial AML/MDS diagnosis.
   - Receiving standard intensive AML frontline chemotherapy starting June 1, 2016 or after.
   - Able to read English or Spanish, if 8 years of age or older

2) Participants will be enrolled as patient-caregiver dyads. The caregiver must be:

   - Able to read English or Spanish.
   - The legal guardian of a patient receiving standard intensive AML frontline chemotherapy starting June 1, 2016 or after .

3) Parental/caregiver informed consent and, if appropriate, child assent.

3.4.1.2 Exclusion Criteria

- Patients being treated for relapsed AML
- Patients with Acute Promyelocytic Leukemia (APML)
- Patients undergoing stem cell transplant (SCT)
- Patients receiving reduced intensity frontline chemotherapy

Any violations of these criteria will be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Participant Identification

Local study investigators (pediatric oncologists and study coordinators) at each of the fifteen participating pediatric institutions will communicate on a weekly basis with their inpatient leukemia service to identify AML or MDS patients potentially eligible for study enrollment. Once identified, study personnel will review each patient for study eligibility criteria.

4.2 Screening Visit

The eligibility criteria for participation will be confirmed prior to approaching for consent. Eligible patients interested in the study will be approached for consent at any time from AML/MDS diagnosis through last day of chemotherapy in the treatment course under study. In some cases, the patient's caregivers may not be present in the hospital to provide consent. In these cases, study personnel will obtain verbal consent from the caregivers and child assent (if appropriate).

4.3 Visit 1

Visit 1 will occur prior to the last day of chemotherapy administration in the course. This visit will include:

- 3 baseline health-related quality of life (HRQOL) PedsQL™ survey modules (core, cancer, and fatigue)
- 2 Brief demographic surveys to capture covariates unavailable in the medical record
- 1 Financial toxicity survey

Surveys will be administered via paper or a smart device and will last a total of 15-30 minutes per respondent. In the case that the child is 5 years of age or older, the child self-report and parent proxy-report scales will be separately administered to the child and caregiver, respectively. If the child is between 5 and 8 years of age, Study Personnel will read the survey questions to the patient. There is an illustrated response aid for these young patients. These age-specific PedsQL instruments have been previously validated. The child will indicate their answer as 'Not at all', 'Sometimes', or 'A lot' by pointing to a smiling, middle, or frowning face, respectively. If the child is under 5 years of age, only the parent-proxy version will be administered. Caregivers will also be asked to complete the demographic covariate surveys and the financial toxicity survey during Visit 1. The brief demographic surveys capture covariates unavailable in the medical record, such 'patient race/ethnicity','patient/parent education level', and 'parent marital status'. The financial toxicity survey assesses the financial situation of the caregiver/family.

4.4 Visit 2

Visit 2 will occur within the period after absolute neutrophil count recovery and ideally prior to the start of the subsequent course of chemotherapy, but no later than the last day of chemotherapy in that next treatment course. For the small number of patients who will begin the next course of chemotherapy before count recovery, Visit 2 will occur within the period from one day prior to the start of chemotherapy in that next treatment course and no later than the last day of chemotherapy in that course. This visit will include:

- 3 follow-up health-related quality of life (HRQOL) PedsQL™ surveys (core, cancer, and fatigue)
- 1 PCO survey
- 1 Financial toxicity survey

All surveys will be administered via paper or a smart device and will last a total of 15-30 minutes per respondent. In the case that the child is 5 years of age or older, the PedsQL child self-report and parent proxy-report scales will be administered to the child and caregiver, respectively. If the child is between 5 and 8 years of age, Study Personnel will read the survey questions to the patient. There is an illustrated response aid for these young patients. These age-specific PedsQL instruments have been previously validated. The child will indicate their answer as 'Not at all', 'Sometimes', or 'A lot' by pointing to a smiling, middle, or frowning face, respectively. If the child is under 5 years of age, only the parent-proxy version will be administered. Caregivers will also be asked to complete the PCO

survey at follow-up. The PCO survey assesses dimensions such as parental stress and anxiety, patient's sleep behaviors, impact on siblings, and hospital discharge teaching practices. In addition, caregivers will be asked to complete the financial toxicity survey again at follow-up. The caregiver completing the follow-up assessments must be the same caregiver who completed the baseline assessments. We will provide a $50 gift card to each child-parent dyad upon completion of the PCO survey, financial toxicity survey, and follow-up quality of life surveys. If the child and caregiver do not complete both visits, they will only be compensated a portion of the $50 for the visits they do complete.

4.5 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to the study plan.

4.5.1 Early Termination Study Visit

Child-caregiver dyads who withdraw from the study during or prior to completion of the follow-up surveys will only be compensated a portion of the $50 for the visits they do complete.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Screening

The following information will be utilized by local study investigators prior to participant approach:

- Date of birth
- Specific leukemia diagnosis and date
- Planned treatment regimens
- Ability to read English or Spanish for all caregivers and for patients 8 years of age or older

Some information will be retained for screened patients who do not enroll to document the reasons for exclusion. Specifically, we will be retaining age, leukemia diagnosis and date, treatment course, and whether the patient received reduced intensity chemotherapy.

5.1.2 Medical Record Abstraction

Medical record abstraction will be performed as per the related Protocol 15-012074 Aim 1: Managing neutropenia in pediatric AML protocol. The table below includes a complete list of the data elements to be abstracted. St. Jude Children's Research Hospital is not participating in Aim 1 and therefore will follow the abstraction process outlined in the Aim 3 Protocol Addendum. The abstracted data elements will be linked to the quality of life and PCO data described in the current protocol.

Variable

Date of birth
Sex
Patient race/ethnicity
Date of AML (or MDS) diagnosis
Age at AML (or MDS) diagnosis
Vital status
Date of death or date of last known follow-up
Location of death (in hospital or at home)
AML subtype
AML risk classification and cytogenetics
Hospital admission start/stop dates
Chemotherapy course number
Chemotherapy regimen and start/stop dates
Course start/stop dates
On COG protocol or similar clinical trial?
Documentation of deviation from planned chemotherapy course
Presence/type of central line
MRD post courses and dates of MRD obtained
Post course remission status
Daily max. fever; how was temperature taken
Infections during chemotherapy courses
ICU care during chemotherapy courses
ANC measurements post chemotherapy
Dates of ANC measurements
Dates and results of microbiological cultures/PCRs onset during post chemotherapy course follow-up
Mucositis severity by course
Systemic antimicrobial prophylaxis at each course
Height, weight, and body surface area at end of chemotherapy course
Nutritional status/supplemental support requirements on day of chemotherapy completion
Ability to practice oral hygiene
Insurance status at course start (private, self-pay, public, other)
English spoken?
Home address
Availability of working telephone
Automobile/taxi voucher requirements
Caregiver's relation to patient
Caregiver's marital status
If caregiver is married, relation between caregiver's spouse and patient
Date of relapse
Site of relapse
Date of transplant
Type of transplant

5.1.3 Evaluations and Measures

Three evaluation tools will be utilized over the two study visits: 2 demographic covariate surveys, PedsQL™ scales, and a PCO Survey.

- **Demographic covariate survey**
  The following patient-level information will be obtained via survey to capture covariates unavailable or less readily available in the medical record:
  - Patient race/ethnicity
  - Parental employment status
  - Household income
  - Parental and patient education level
  - Number of adults living in the primary residence
  - Number of other children living in the primary residence

- Demographic covariate survey II

The following patient-level information will be obtained via survey to capture covariates unavailable or less readily available in the medical record:

- Parent/legal guardian who signed informed consent
- Relation to patient (i.e. mother, father, other)
- Parent/legal guardian marital status

- **PedsQL™**
  HRQOL will be assessed using the following validated PedsQL™ scales:
  - The 23-item multidimensional 4.0 Generic Core Scales:
    - Physical functioning (8 items)
    - Emotional functioning (5 items)
    - Social functioning (5 items)
    - School functioning (5 items)
  - The 18-item multidimensional Fatigue Scale:
    - General fatigue (6 items)
    - Sleep/rest fatigue (6 items)
    - Cognitive fatigue (6 items)
  - The 27-item multidimensional 3.0 Cancer Module:
    - Pain/hurt (2 items)
    - Nausea (5 items)
    - Procedural anxiety (3 items)
    - Treatment anxiety (3 items)
    - Worry (3 items)
    - Cognitive problems (5 items)
    - Perceived physical appearance (3 items)
    - Communication (3 items)

- **Financial toxicity survey**
  - 11-item survey that assesses the financial situation of the caregiver/family. Items inquire about:
    - Having enough money to cover cost of child's treatment

- Out-of-pocket expenses exceeding their expectations
- Worrying about future financial problems
- Feeling like have no choice about amount spent on care
- Feeling frustrated that cannot work or contribute as much as usual
- Satisfaction with current financial situation
- Ability to meet monthly expenses
- Feeling financially stressed
- Concern about keeping job and income
- Overall control of financial situation

The format, instructions, response scale and scoring methods for the three PedsQL scales are identical. Each is available in parallel child self-report and parent proxy-report formats. Child self-report versions include ages 5-7 years, 8-12 years and 13-18 years. Parent proxy report versions include ages 1-2 years, 2-4 years, 5-7 years, 8-12 years and 13-18 years. In this study we will administer the Child Self-Report versions of the scales for children 5 years of age and older in addition to the Parent Proxy-Report versions.

A 5-point Likert response scale is used across child self-report for ages 8-18 and parent proxy-report (anchored by 0 = never a problem to 4 = almost always a problem). Responses to each question are used to assemble a score.

Each of these scales demonstrates internal reliability acceptable for group comparisons (PedsQL™ Generic Core Total Scale Score [Cronbach's $\alpha = 0.88$ child, 0.93 parent report]; Multidimensional Fatigue Total Scale Score [$\alpha = 0.89$ child, 0.92 parent report]; most Cancer Module Scales [average $\alpha = 0.72$ child, 0.87 parent report]) (29). These scales have also been shown to be sensitive to change over time in children with cancer (30).

- **PCO Survey**
  - Pediatric Inventory for Parents-Difficulty scales (PIP-D)-(42 items)
  - Parental stress and anxiety (9 items)
  - Sleep Disturbance Scale for Children (SDSC): Disorders of Initiating and Maintaining Sleep domain (DIMS) (7 items)
  - Impact on Siblings (7 items)
  - Hospital Discharge Teaching Practices (4 items)

The PCO survey will be completed by the parent during study Visit 2. The PCO includes established measures of parental stress (PIP-D) and sleep disturbance in children (SDSC DIMS) as well as survey questions designed to measure the incidence and sources of parental financial stress; sources of parenting, emotional, domestic and financial support; the incidence and nature of sibling behavioral change, and the receipt of training prior to discharge from the hospital.

The PIP-D assesses stress-related difficulty with events faced by parents of children with serious illness across four domains: communication (e.g., with child, partner, or health care team), emotional functioning (e.g., impact of illness on sleeping and mood), child's medical care (e.g., carrying out medical regimen), and role functioning (e.g., impact of illness on

parent's ability to work and care for other children). All items are rated on a five-point Likert scale from 1 (not at all difficult) to 5 (extremely difficult) (31).

The SDSC DIMS assesses sleep indices such as latency and duration, night awakenings, and reluctance to go to bed. All items are measured on a five-point Likert scale, in which 1= never, 2= occasionally, 3= sometimes, 4= often, and 5= always. The SDSC is reported to have high internal consistency among both healthy (α=0.79) and sleep disordered participants (α=0.71), as well as high test–retest reliability (r=0.71) (32).

- **Financial toxicity survey**

The financial toxicity survey will be completed by the parent at both baseline and follow-up (Visit 1 and Visit 2). The survey includes 11 statements about the financial situation of the caregiver/family in relation to the child's treatment adapted from existing literature (37). A 5-point Likert response scale is used for the parent to indicate the degree to which they agree with each statement (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; 4 = Very much).

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary outcome of interest will include the following endpoint:

- Scores of HRQOL obtained from the PedsQL™ scales

The secondary outcomes of interest will include the following:

- Scores of difficulty with events faced by parents of children with serious illness from the PIP-D
- Scores for patient sleep behavior from the SDSC DIMS
- Incidence and sources of parental financial distress following patient's AML/MDS diagnosis
- Incidence of sibling behavior change following patient's AML/MDS diagnosis
- Financial toxicity scores obtained from the financial toxicity survey

6.2 Control of Bias and Confounding

This is an observational cohort study, so subjects are not assigned by a process of randomization and are therefore subject to bias. However, analyses of our data will control for potential confounding by various patient- and hospital- level factors. Additionally there is a possibility of exposure misclassification given that patients who are discharged more than 3 days after chemotherapy completion but well before neutropenia recovery will still be included in the inpatient management group. To account for this imperfect specificity, sensitivity analyses will be performed utilizing a less strict threshold for discharge classification (e.g., 5 or 10 days post-chemotherapy).

6.3 Statistical Methods

6.3.1 Analysis of Primary Outcomes of Interest

Propensity score analyses will be used to adjust for potential confounding by baseline covariates. First, bivariate analyses will be performed to evaluate relationships between each baseline covariate and neutropenia management strategy as well as each outcome of interest. Next, propensity scores will be derived from the predicted probabilities estimated from logistic regression models of the use of outpatient versus inpatient management during neutropenia conditional on all baseline factors determined to be true confounders (i.e., those associated with both exposure and outcome) and those determined to be potential confounders (i.e., those associated only with the outcome interests). Patients will then be stratified into five groups using quintiles of the estimated propensity score. The distributions of exposure within the quintiles will be examined for sufficient sample sizes and balance. Within each stratum, the patients managed as outpatient and those managed as inpatient will ideally have similar values of the propensity score and likewise the distribution of measured baseline covariates will be comparable between them.

PedsQL™ items will be reverse scored and linearly transformed to a scale of 0 to 100 such that higher scores will be reflective of better HRQOL. The PedsQL™ total score will be calculated as the sum of the item-specific scores divided by the number of answered items (33, 34).

We will utilize linear mixed effect models to test the association between neutropenia management strategy and the PedsQL™ total score. Specifically, the two repeated measures of the PedsQL™ total score will be the outcome and regressed on time, group (outpatient versus inpatient) and interaction between time and group will be the fixed effects, and a subject level random effect will be included to account for the potential correlations between the repeated measures. Such mixed models are more powerful than ANCOVA or analysis of change scores, and they benefit from the added power arising from any correlation of repeated measures over time. A significant group by time interaction will suggest that the change of PedsQL™ is different between the two groups. Adjustment for differences in covariates across neutropenia management groups will be accomplished through the propensity score outlined above, and by controlling for confounding of any remaining unbalanced potential confounders. Secondary analyses will be performed for the cancer and fatigue modules as well as for the physical and psychosocial subscales of the PedsQL™.

6.3.2 Analysis of Secondary Outcomes of Interest

Responses to each of the items on the PIP-D were summed to obtain a total score reflecting the amount of difficulty experienced when handling events faced by parents of children with serious illness. Higher scores indicate greater difficulty and increased pediatric parenting stress (31).

Responses to each of the items on the SDSC DIMS subscale are summed to get a total domain score that is mapped to a corresponding T-score using the SDSC scoring sheet. Higher T-scores are reflective of greater clinical severity of symptoms and a T-score greater than 70 is considered pathological (32). For the PCO, we will utilize appropriate standard statistical methods to evaluate the relationships with neutropenia management strategy

(outpatient versus inpatient). For binary outcomes, log-binomial regression with robust error estimates will be employed to obtain risk ratios (95% CI). For continuous outcomes, generalized linear models will be used incorporating the appropriate distribution based on a graphical assessment of the outcome data. All models will be adjusted for baseline propensity scores by quintiles. Log-binomial regression with robust error estimates will also be employed to obtain risk ratios (95% CI) comparing the incidence of any financial toxicity (versus none), separately for each item on the financial toxicity survey as well as overall across all survey items. For the total score obtained from the financial toxicity survey, we will utilize methods comparable to those described for the PedsQL™ total score in section 6.3.1 above.

6.4 Sample Size and Power

We expect to prospectively identify approximately 139 patients and assuming 90% of identified patients will be discharge eligible and 85% will consent, the anticipated study population will be 118patients and their caregivers. Approximately 40% will be managed as outpatients, so we expect 47 outpatients and 71 inpatients. The power calculation was conducted under the framework of a multivariate general linear hypothesis for general linear models, using the Wilks Lambda test with a significance level of 0.05 (35, 36). Assuming a standard deviation (SD) of 20 for the PedsQL™ total score, if there is no correlation we will have 80% power to detect a large effect size of 0.75 that is a 15.0 point difference in the mean change scores between the two groups. If the correlation is as high as 0.8 we will have 80% power to detect a small effect size of 0.34, that is a 6.8 point difference in the mean change scores between the two groups.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study, though no adverse events are expected to result from the work proposed in this protocol.

7.2 Adverse Event Reporting

Since the study procedures are not greater than minimal risk, SAEs are not expected. If any unanticipated problems related to the research involving risks to subjects or others occur during the course of this study (including SAEs) these will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8 STUDY ADMINISTRATION

8.1 Data Collection and Management

These data will consist of patient and caregiver responses to the demographic surveys, HRQOL PedsQL™ scales, PCO survey, and financial toxicity survey. These scales will be administered via paper or by using the LSTcare application via a tablet computer or other smart device. The PedsQL™ scales are described above in Section 5.1.3. Survey responses collected through the LSTCare™ are maintained in a Software as a Service (SaaS) model. LSTCare™ is fully compliant with all HIPAA regulations. Additionally, LST has contracted with FireHost Secure Cloud Hosting based in Dallas, Texas, to host and manage all computer systems and networks. FireHost is a leader in HIPAA compliant Secure Cloud Hosting and delivers hosting solutions to eCommerce, SaaS, Healthcare IT and Security Companies around the world. Data are encrypted between the device and the back end services and the data are available via LST secured web application and via written queries and downloadable spreadsheets. The PCO survey and financial toxicity survey are described in Section 5.1.3, and will be administered on paper or by using REDCap™ via a public survey link. When screening patients to determine their eligibility, medical record data will be abstracted and entered electronically directly into a REDCap™ database, a secure, web-based application designed exclusively to support data capture for research studies. The REDCap™ database is designed so that local investigators cannot see data entered by other sites. We will utilize REDCap™ automated export processes to seamlessly download the chart abstraction data for review and analysis. All statistical output and generated data files, tables, and figures will be stored in password protected files on a secure server, which is automatically backed up each night. A unique study identification number will be assigned to participants so that no study file contains identifiable information. A master list linking the study identification number to the individual participant will be stored in a password protected file on a secure drive. Identifiers will be destroyed after publication. If surveys will be completed on paper, CHOP research personnel will enter all data captured via paper forms into the corresponding electronic study databases. Data entry will be quality checked by a second study team member. Electronic scans of the completed paper assessments will be saved on a secure server for up to one year following study completion and all paper forms will be immediately destroyed once scanned and entered into the study database.

8.1.1 Data sources

Local investigators will query their site's AML/MDS registry, and if necessary patients' electronic medical records, for demographic information, clinical information, and hospital admission/discharge dates. The complete list of variables is detailed in Section 5.1.1 and 5.1.2. Patient and caregiver perspectives on neutropenia management strategy and their reports of health related quality of life will be obtained via PedsQL™ modules described in Section 5.1.3. Additional outcomes including parental stress and anxiety, patient's sleep behaviors, impact on siblings, and hospital discharge teaching practices will also be measured via the PCO survey also described in Section 5.1.3. Financial toxicity will be assessed via the survey described in Section 5.1.3.

8.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. No identifiable data will be used for future study without first obtaining IRB approval. CHOP will receive data from each participating site, but before sharing a limited dataset with other researchers (including those at CHOP) the investigator will obtain a data use agreement between the PI and any recipient researchers. Safeguards to protect confidentiality were described above in Section 8.1 and are also detailed below in Section 8.3.2.

8.3 Regulatory and Ethical Considerations

8.3.1 Data and Safety Monitoring Plan

Given the types of data and the observational study design, specifically the absence of an imposed intervention, we do not anticipate needing to utilize a data safety and monitoring plan. However, in the unlikely event of a participant necessitating psychological treatment due to adverse effects of study participation, a member of the research team will make appropriate referrals within CHOP or the external healthcare facility. The investigators are experienced in talking with parents who are under the stress of a child's illness and with children in medical settings.

8.3.2 Risk Assessment

This is a minimal risk study. There are no new patient interventions or treatments associated with the work outlined in this proposal. As such, there are no expected additional health risks that a patient would incur as a result of participation in this study. The medical care of subjects will not be affected in any way by their participation in this study. Similarly, the medical care of those who choose not to participate in this study will also be unchanged.

There may be a small risk of discomfort or anxiety for the patients and/or caregivers while engaging in the surveys. To protect against discomfort of the child or caregiver during the survey administration we will take multiple steps. First, we will administer the surveys at a time and location of the respondent's choosing. Second, we will let our respondents know that they can discontinue the survey at any time, for any reason, without penalty to them.

Another possible risk is the loss of confidentiality. We will institute strict procedures to maintain confidentiality. All data and personally identifiable information will be stored electronically on a secure server in password protected files. None of the survey responses on paper or electronic forms will contain patient identifiers. We will record all identifier information on a separate form. A unique study identification number will link the baseline health-related quality of life (HRQOL) PedsQL™, demographic surveys, and financial toxicity survey to the follow-up HRQOL PedsQL™, PCO survey, and the financial toxicity survey. A master list linking study identification to the individual will be stored in a password protected file on a secure drive. Any paperwork will be kept in study binders in locked file cabinets in offices with locked doors. All electronic files will be stored on password protected computers in locked offices. Entry to the offices is controlled at a main

entrance by identification card readers. Research materials will be accessible only to members of the investigative team. Access by members of the research team to any patient identifiers will be limited to the minimum necessary to carry out the proposed research. Any publications or presentations resulting from this work will not identify participants by name, but will only present aggregate data. Our prior research employing similar precautions has demonstrated that these techniques are very successful in assuring the protection of subjects.

8.3.3 Potential Benefits of Study Participation

The patients involved in the study might not benefit directly, except if a survey response improves the patient's understanding of his or her course and promotes additional contact with his or her clinicians. Results from the study may be applied in the future to AML/MDS patients in making decisions about the best way to manage neutropenia. Improved understanding of the outcomes as well as caregiver/patient perspective of outpatient versus inpatient management of neutropenia will be of great importance to AML/MDS patients and the providers who care for them.

8.3.4 Risk-Benefit Assessment

As minimal risk research, the risks to the subjects are reasonable with respect to the knowledge that may result from the research.

8.4 Recruitment Strategy

Local study investigators (pediatric oncologists and study coordinators) at each of the fifteen participating pediatric institutions will communicate on a weekly basis with their inpatient leukemia service to identify AML and MDS patients potentially eligible for study enrollment. Once identified, study personnel will review each patient for study eligibility criteria. The eligibility criteria for participation will be confirmed prior to approaching for consent. Eligible patients interested in the study will be approached for consent at any time from AML/MDS diagnosis through last day of chemotherapy in the treatment course under study.

8.5 Informed Consent/Assent and HIPAA Authorization

If interested in participation, parents will be given a thorough explanation of the study including the purpose, procedures, risks and benefits of participation, confidentiality, procedures for withdrawal, reimbursement, and contact information for study personnel. Families will be informed that their medical care at CHOP or any another healthcare facility will not be affected if they choose not to participate in the proposed research. After reviewing eligibility we will obtain informed consent and HIPAA authorization from parents, and if age eligible, we will seek child assent. The assent process with children will include a developmentally appropriate explanation of the purpose of the research, what research participation entails, and procedures for withdrawal from the study. Children will be informed that their participation is voluntary and that they can withdraw from the study at any time. Informed consent/assent and HIPAA Authorization will take place in a quiet, private space to ensure confidentiality and the family will be provided ample time to make an informed and thoughtful decision. Combined informed consent-HIPAA authorization documents will be used.

8.5.1 A Waiver of Documentation of Consent and Alteration of HIPAA Authorization (to obtain verbal authorization)

In some cases, the patient's caregivers may not be present in the hospital to provide consent. In such cases, study personnel will obtain verbal consent from the caregivers and written assent for the child (if age appropriate). Verbal consent will be obtained on the telephone. The study personnel obtaining verbal consent will be in a quiet, private space to ensure confidentiality and the family will be provided ample time to make an informed and thoughtful decision. Combined verbal consent-HIPAA Authorization documents will be used. A copy of the verbal consent form will be provided to the caregiver via mail or email. After verbal consent is obtained from the caregiver, the study personnel will obtain written assent from the child, if age appropriate. The process for obtaining written assent is described in section 8.5.

8.6 Financial Information

8.6.1 Payments to subject for time, effort and inconvenience (i.e. compensation)

Following completion of both the baseline surveys (PedsQL™, demographic surveys, and financial toxicity survey) and follow-up surveys (PedsQL™ modules,PCO survey, and financial toxicity survey), child-parent dyads will be compensated with a $50.00 gift card. If the child and caregiver do not complete both visits, they will only be compensated a portion of the $50 for the visits they do complete.

8.6.2 Who is funding this research study?

The Patient Center Outcomes Research Institute provided funding for this study until February 28, 2019. Effective March 1, 2019, CHOP is funding the study.

9 PUBLICATION

The results of this study will be prepared and submitted to peer-reviewed journals. The compiled de-identified data from this study will be maintained by CHOP investigators. Thus all submitted manuscripts will be directed by these CHOP investigators. Any data presented will be presented in summary form and there will be no potential for patient identification through a publication.

Additionally, to optimize the dissemination of our study results to patient and caregivers we will work with two organizations: Alex's Lemonade Stand Foundation (ALSF) and the COG Patient Advocacy Committee (PAC). Throughout the 2.5 year study we will hold several Board meetings with both ALSF and the COG PAC to share our research findings and elicit their feedback on the best way to communicate, disseminate and translate our research findings into a format that will be useful (and available) to patients and their caregivers when they are faced with a decision about what kind of neutropenia management strategy is best for them.

Because children with AML/MDS and their caregivers are participants in the study we will also share our study results with them. At the conclusion of their participation we will ask if

they are interested in receiving information about what we find in our study. If they say yes, we will send them a newsletter summarizing the results of our study via mail, created in collaboration with our patient stakeholder partners.

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