Title:	**Home or away from home: comparing clinical outcomes relevant to the care of pediatric acute myeloid leukemia or myelodysplastic syndrome during periods of neutropenia**
Short Title:	Aim 1: Managing neutropenia in pediatric AML/MDS
NCT Number:	NCT02774850
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ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATIONS

AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
CHOP	The Children's Hospital of Philadelphia
CI	Confidence Intervals
COG	Children's Oncology Group
ICU	Intensive Care Unit
MDS	Myelodysplastic syndrome
PCORI	Patient-Centered Outcome Research Institute
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

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.

Objectives:

The primary objective of this study is to compare the clinical effectiveness of outpatient versus inpatient management of neutropenia in children with AML or MDS receiving standard intensive AML frontline chemotherapy.

Study Design:

This is a bidirectional observational cohort study.

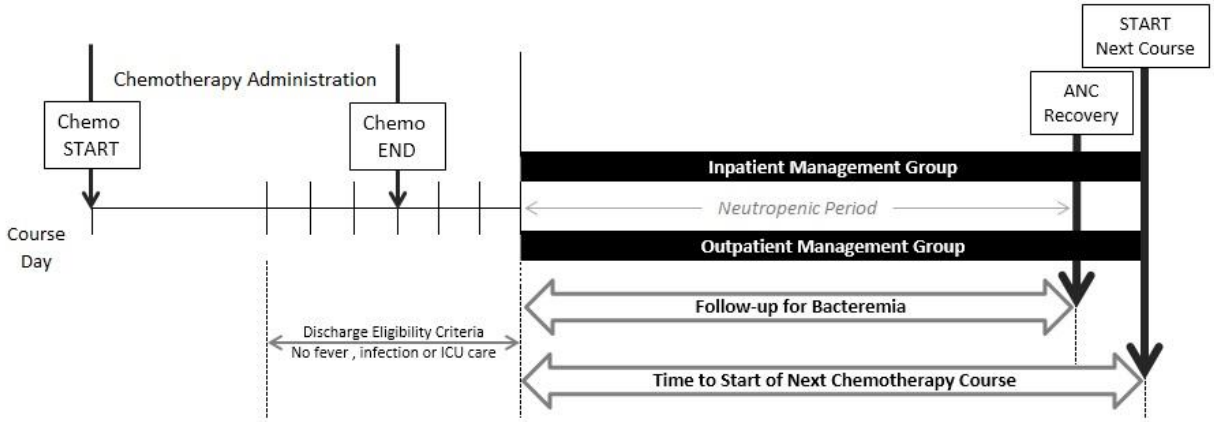
Setting/Participants:

Participants will be less than 19 years of age at their initial AML or MDS diagnosis receiving or having received frontline AML chemotherapy from seventeen participating pediatric hospitals across the United States (US). We anticipate that approximately 540 subjects will be evaluable for chart abstraction over the study period in order to study clinical outcomes including the occurrence of bacteremia and time to the start of the next course in the chemotherapy regimen, in relation to neutropenia management strategy.

Study Interventions and Measures:

There is no study intervention. Main outcomes include occurrences of bacteremia after completion of an AML chemotherapy course, and time from completion of one course to the next planned course of chemotherapy.

FIGURE 1: STUDY DIAGRAM



ANC= absolute neutrophil count
ICU= intensive care unit

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).

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) (2). 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 (3, 4) with bacteremia constituting the most prevalent infection (5). These infectious complications remain a major cause of therapy-associated morbidity and mortality in children with AML (6, 7).

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" (8). 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. 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 (9, 10). This variation in practice highlights the need for additional data on clinician-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 (23). 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 (11-18). Additionally, early discharge of adult AML patients receiving chemotherapy has been associated with fewer and shorter febrile episodes (15, 19), a better response to first line antibiotics, and shorter duration of intravenous antibiotic administration (13, 15, 18, 19). 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 (20). 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.

In order to appropriately inform the decision for outpatient versus inpatient management of neutropenia associated with pediatric AML chemotherapy, a comprehensive study that collects pertinent clinical outcomes is necessary. Given that infectious complications are the leading cause of treatment related mortality among AML patients (22) and among MDS patients (24, 25), identifying such a neutropenia management strategy that leads to the best clinical outcomes will have a substantial impact on care of these patients.

Bacteremia, a cause of transient cardiac decline, occurs frequently during AML treatment and contributes to the development of cardiac dysfunction.(26) COG guidelines for re-challenging patients to anthracycline chemotherapy distinguish infection-associated LV systolic dysfunction (LVSD) from LVSD not associated with infection, allowing patients who experience resolution of infection-associated LVSD to receive additional anthracycline therapy. However, there are no data comparing the longitudinal trajectories of EF/SF or the impacts on subsequent cardiomyopathy and treatment outcomes for these distinct presentations of cardiotoxicity.

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 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 compare the effectiveness of outpatient versus inpatient management of AML neutropenia or MDS in individuals receiving standard AML frontline chemotherapy. We plan to accomplish this through the following Objectives:

2.1 Primary Objectives

2.1.1 Compare the incidence of bacteremia among children with AML or MDS receiving standard intensive AML frontline chemotherapy monitored in the outpatient setting during neutropenia ("early discharge") relative to those who remain hospitalized ("inpatient").

2.1.2 Compare the length of time to initiation of the subsequent chemotherapy course between children with AML or MDS receiving standard intensive AML frontline chemotherapy monitored in the outpatient setting during neutropenia to similar children who remain hospitalized.

2.2 Secondary Objectives

2.2.1 Identify subpopulations based on distinct longitudinal patterns of LV ejection fraction (EF) and fractional shortening (SF) decrease and recovery and evaluate the impact of bacteremia on the longitudinal patterns of LVEF and LVSF. Compare relapse risk (RR) and OS in subgroups.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This observational cohort study will evaluate clinical outcomes of inpatient versus outpatient management of neutropenia following chemotherapy in children with AML or MDS by abstracting data from medical records.

3.2 Study Duration, Enrollment and Number of Sites

The study plans to include patients treated for AML or MDS anytime from January 1, 2012 or after.

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

3.3.1 Duration of Study Participation

No direct patient contact is necessary for this study; only medical record abstraction. The chart abstraction window for each participant will include the time period from the start of the first course of chemotherapy until the date of last patient contact or death.

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

Chart abstraction will be conducted at the following seventeen US investigative sites: Ann Arbor (*C.S. Mott Children's Hospital*), Atlanta (*Children's Healthcare of Atlanta*), Chicago (*Ann & Robert H Lurie Children's Hospital of Chicago*), Dallas (*Children's Medical Center of Dallas – University of Texas Southwestern Medical Center*), Detroit *(Children's Hospital of Michigan)*, Houston (*Texas Children's Hospital*), Jackson *(Children's of Mississippi)*, Little Rock (*Arkansas Children's Hospital*), New Orleans (*Ochsner Medical Center for Children*), Palo Alto (*Lucile Packard Children's Hospital Stanford*), Philadelphia (*Children's Hospital of Philadelphia*), Salt Lake City (*Primary Children's Medical Center*), San Diego (*Rady Children's Hospital*), Seattle (*Seattle Children's Hospital*), Denver *(Children's Hospital of Colorado),* 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 (inpatient versus outpatient).

We expect to identify a total of approximately 600 newly diagnosed AML patients across the seventeen participating institutions over the study period of which approximately 540 are expected to meet early discharge eligibility criteria.

3.4 Study Population

The study population will include all AML and MDS patients who received or will receive chemotherapy starting January 1, 2012 at any of the seventeen participating pediatric institutions across the US. Patients discharged within 3 days after completion of that chemotherapy course will be categorized as 'early discharge' to outpatient management during neutropenia. Patients meeting eligibility criteria for 'early discharge' but remaining in the hospital more than 3 days after completion of that chemotherapy course will be categorized as inpatient management. Patients will be considered early discharge-eligible if there is no evidence of fever, infection or intensive care unit (ICU) level care within ± 3 days of the last dose of chemotherapy.

3.4.1Aim 1 Inclusion Criteria

1) Males or females less than 19 years of age at initial AML/MDS diagnosis.

2) Receipt or planned receipt of standard intensive AML frontline chemotherapy any time from January 1, 2012 or after.

3.4.2Aim 1 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

4 STUDY PROCEDURES

4.1 Aim 1

The only study procedure for this cohort is chart abstraction; thus, there will be no study visits or other patient contact encounters required from the participant.

4.1.1 Retrospective Patient Identification:

Local study investigators (pediatric oncologists and study coordinators) at each of the seventeen participating pediatric institutions will review their hospital AML or MDS registry to identify patients from January 1, 2012 through the date of IRB approval that meet enrollment criteria.

4.1.2 Prospective patient identification:

The prospective data abstraction timeline begins the date of IRB approval and lasts through the duration of the study. Study investigators at each institution 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.

4.1.3 Data Abstraction

For all enrolled patients, chart abstraction will be performed by CHOP personnel or local site staff using standardized data abstraction processes. Trained CHOP study personnel will first abstract data for CHOP patients identified between January 1, 2012 and date of IRB approval. They will then travel to the other 16 sites to assist and educate local study personnel on the chart abstraction procedures for patients identified at those institutions. Alternatively, CHOP personnel can perform medical record abstraction remotely for sites who grant CHOP remote EMR access. All data will be abstracted directly into REDCap™ via standardized electronic case report forms developed by CHOP study personnel. Details on data to be abstracted from the medical record are included in sections 5.1.1 and 6.1 below.

4.2 Subject Completion/Withdrawal

This is an analysis of data that are documented in the course of providing clinical care to subjects. As there are no additional interventions necessary for the execution of this study and we do not foresee any adverse effects stemming from the research, a waiver of consent will be submitted to address the issue of subject withdrawal.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

The following variables will be abstracted from the medical chart:

Variable
Date of birth
Sex
Patient race/ethnicity
Date of AML/MDS diagnosis
Age at AML/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
Chemotherapy regimen and start/stop dates
Course start/stop dates
Clinical trial enrollment and specific protocol
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 by course
Systematic antimicrobial prophylaxis at each course
Height, weight, and body surface area at start 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
Date of relapse
Site of relapse
Date of transplant
Type of transplant
Echocardiographic evaluations (e.g., dates, resulting measurements, measurement mode)
Blood pressure and heart rate at echocardiographic evaluations
Dexrazoxane administration
Malignant blast percentage

Bone marrow malignant blast percent
Empiric/definitive anti-infective use
Preferred language
Treatment and positive blood cultures at outside hospital (y/n)
Down Syndrome diagnosis
CNS status at the end of each course
Outpatient encounters (e.g., clinic/day hospital, ED)

Some information will be retained for all screened patients to document the reasons for ineligibility. Specifically, we will be retaining information on age, leukemia diagnosis, treatment course, and whether the patient received reduced intensity chemotherapy.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary outcomes will include the following two endpoints (ascertained from patient medical records):

1.) Occurrence of post-chemotherapy bacteremia
Identification of bacteremia will begin three days after completion of a chemotherapy course and will continue until recovery of neutrophil count (ANC > 200 μL), or until the start of the next course (for a very small number of patients who begin the next course of chemotherapy prior to count recovery). Bacteremia will be defined as a single positive blood culture for a bacterial pathogen (including Viridans group Streptococci). If the bacterium is an organism considered as a common commensal organism by the National Healthcare Safety Network, two separate positive blood cultures will be required for classification as bacteremia.

2.) Time to the initiation of the next chemotherapy course
Time to next course of chemotherapy will be measured as the number of days from the three days after the completion chemotherapy in a given course until the first day of the next course.

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.

Log-binomial regression will be used to estimate risk ratios with 95% confidence intervals (CI) comparing the incidence of bacteremia following outpatient versus inpatient neutropenia management strategy. Control for confounding will be accomplished through adjustment for propensity score by quintiles as well as any remaining unbalanced patient- or hospital-level confounders.

Generalized linear regression models will be utilized to compare time (in days) from three days after completion of one chemotherapy course to initiation of the next course of chemotherapy by neutropenia management strategy (outpatient versus inpatient). Before model fitting, the normality of the outcome will be assessed. If the normality assumption holds, then traditional linear models (normal distribution with an identity link) will be utilized. If the distribution of time to next course is significantly skewed, then models assuming a gamma or log-normal distribution as appropriate will be used. Again, control for confounding will be accomplished through adjustment for propensity score by quintiles as well as any remaining unbalanced confounders.

Although there will be limited power to quantify heterogeneity of effects across strata of covariates, hypothesis-generating subanalyses will be performed to evaluate the potential for effect measure modification (on both absolute and relative scales) by age, race, and insurance status (as a proxy for socioeconomic status) via stratification to inform future studies.

6.3.1 Analysis of Secondary Outcome of Interest

One secondary outcome of interest is LV function quantified as EF and SF over the courses of therapy and post-treatment follow-up. LVEF and LVSF trajectories will be determined by group-based latent trajectory modeling, a type of structural equation modeling which identifies distinct clusters of individuals based on development, progression, and resolution patterns pertaining to the repeated measures of a given variable. The following factors will be explored as predictors identified trajectory phenotypes: age, gender, race, ethnicity, weight group, presenting white blood cell count, and baseline EF/SF. Univariate and

multivariable mixed effects regression models will be fitted to quantify the association between bacteremia and longitudinal EF and SF measurements.

6.4 Sample Size and Power

Assuming 100% capture of eligible patients (waivers of consent obtained from all participating sites), we expect to identify a total of 600 newly diagnosed AML/MDS patients across the seventeen participating centers. Assuming 90% of identified patients will be early discharge eligible, the anticipated study population will be 540 patients. Based on the rates for the individual participating sites, approximately 27% of the study population will be managed as outpatients (n= 146) and the remaining will be managed as inpatients (n=394) during neutropenia. Assuming a baseline risk of bacteremia of 60%, the proposed size of the two study arms would provide greater than 80% power to detect a 13% difference in bacteremia rates among patients managed as outpatients versus those that remain hospitalized, with a significance level of 0.05. A 13% difference in bacteremia rates would also be a clinically significant difference. For time to next chemotherapy course, we used a two sample t-test in the power calculation to be conservative (i.e., statistical analysis using a generalized linear model with correct distribution will result in creased power over a t-test). Assuming each patient contributes one treatment course and an average time to next chemotherapy course of 29 days and a standard deviation (SD) of 10 (based on preliminary data), our study will have 85.0% power to detect a difference of 3 days between the two groups, with a significance level of 0.05.

7 SAFETY MANAGEMENT

7.1 Clinical Adverse Events

As this is a medical record review, there is no possibility of a clinical adverse event (AEs).

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 happen 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

Medical record data will be abstracted directly into electronic case report forms via REDCap™, a secure, web-based application designed exclusively to support data capture for research studies. We will utilize REDCap™, automated export processes to seamlessly

download the chart abstraction data to statistical packages 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. Each site will maintain their own master list linking each patient's unique study identification number to their medical record number. These site master lists will be stored in password-protected files that are only accessible by approved local study personnel. Identifiers will be destroyed after publication. Access to identifiable information by investigators, programmers, analyst, and statisticians will be kept to the minimum necessary mandated by HIPAA regulations. Coded, limited data sets will be shared with participating sites upon approved request, as specified in Section 8.2. Only aggregate level data will be shared with the study sponsor PCORI.

8.1.1 Data sources

Patients' electronic medical records will be queried for demographic information, clinical information, and hospital admission/discharge dates. The complete list of variables is detailed in Section 5.1.1.

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. The investigator will obtain a data use agreement between provider (the PI) and any recipient researchers (including others at CHOP) before sharing a limited dataset (dates and zip codes). Safeguards to protect confidentiality were described in Section 8.1 and are also detailed 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, there will be no Data and Safety Monitoring Board associated with this study. However, if any risks are identified, the Principal Investigator will notify the IRB promptly.

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.

An unlikely but possible risk is the loss of confidentiality. We will institute strict procedures to maintain confidentiality. Each site will maintain their own master list linking each patient's unique study identification number to their medical record number. These site master lists will be stored in password-protected files that are only accessible by approved

local study personnel. Identifiers will be destroyed after publication. 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 to identifiable information by investigators, programmers, analyst, and statisticians will be kept to the minimum necessary mandated by HIPAA regulations 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. 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 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

This is an analysis of data that are documented in the course of providing clinical care to subjects. There are no additional interventions necessary for the execution of this study and thus there is minimal risk involved with respect to the knowledge that may result from the research.

8.4 Recruitment Strategy

No advertising will be done for this study. Local study investigators (pediatric oncologists and study coordinators) will review their hospital's AML registry to identify newly diagnosed AML and MDS patients in the retrospective period of the study. For the prospective component, local study investigators will identify newly diagnosed AML/MDS patients from weekly communications with the local inpatient leukemia service.

8.5 Informed Consent/Assent and HIPAA Authorization

8.5.1 Waiver of Consent

A full waiver of consent will be requested from the Institutional Review Board. This is an observational study and therefore complete capture of all events is ideal to ensure accurate and unbiased results. It would be impracticable to obtain consent from all eligible patients as it would require obtaining consent from parents of critically ill children, some of whom would certainly refuse to participate in a research study. Some of the patients may no longer be followed at the given institution, or may have moved out of the area, thus up-to-date contact information may not be available. Each site will submit for a waiver of consent at their respective institutions.

For those sites that do not enter into a cooperative agreement with the CHOP IRB, and a waiver of consent is not granted for prospective data collection, parents will then be given a thorough explanation of the study including the purpose, risks and benefits of participation, confidentiality, and contact information for study personnel. Families will be informed their medical care at that healthcare facility will not be affected if they choose not to participate in

the proposed research. Any site-required informed consent/assent and HIPAA Authorization will take place in a quiet, private space to ensure confidentiality, the family will be provided ample time to make an informed and thoughtful decision, and the signed document will be maintained at the local site in a secure location.

8.5.2 Waiver of Assent

A full waiver of assent will be requested to collect the electronic health record of subjects. This is an observational study and therefore it is necessary to include all patients to ensure accurate and unbiased estimates.

8.5.3 Waiver of HIPAA Authorization

A full waiver of HIPAA Authorization will be requested for comprehensive collection of pertinent clinical outcomes. It would be impracticable to obtain consent from all eligible patients as it would require obtaining consent from parents of critically ill children, some of whom would certainly refuse to participate in a research study. Study subjects may no longer be followed at clinic or may have moved out of the area, thus up-to-date contact information is not available. This is an observational study and thus complete capture of all events is ideal to ensure accurate and unbiased results.

8.6 Payment to Subjects/Families

There will be no reimbursement or gifts supplied to patients in this 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.

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