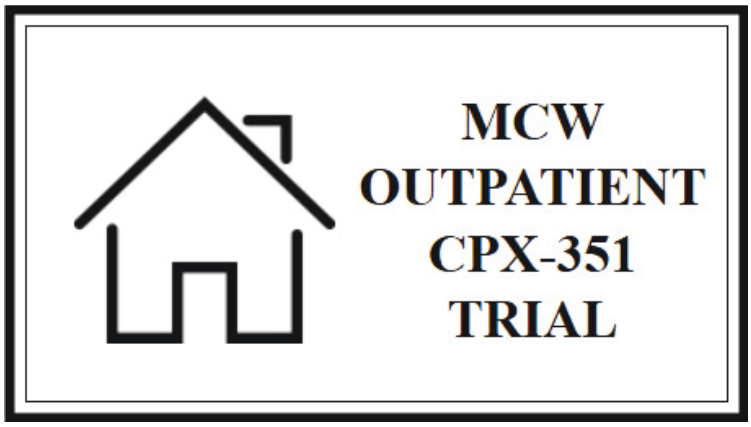
MEDICAL COLLEGE OF WISCONSIN
CANCER CENTER

A multi-institutional, phase IV project to study the feasibility of safely managing patients receiving induction with liposomal daunorubicin and cytarabine (CPX-351) for acute myeloid leukemia (AML) in an outpatient environment

Short Title: Outpatient CPX-351



Principal Investigator (Sponsor)

Laura C. Michaelis, MD

Funding Source

Jazz Pharmaceuticals, Inc.

Current Version Number and Date

Version 3 04/15/2020

Proprietary and Confidential

Title: A multi-institutional, phase IV project to study the feasibility of safely managing patients receiving induction with liposomal daunorubicin and cytarabine (CPX-351) for acute myeloid leukemia (AML) in an outpatient environment

MCW OnCore No.: IIT-Michaelis-OutpatientCPX-351
Jazz Pharmaceuticals Protocol No.: IST-18 10663

Important Note:
The Multisite Coordinator is the main point of contact for any protocol questions or clarifications. Please only contact the Study Principal Investigator if directed by the protocol.

MCW Study Principal Investigator
Laura C. Michaelis, MD
Medical College of Wisconsin
9200 W. Wisconsin Ave. C4191
Milwaukee, WI 53226
Phone: 414-805-4600
Fax: 414-805-4606
Email: lmichaelis@mcw.edu

Biostatistician
Aniko Szabo, PhD
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee, WI 53226

Multisite Coordinator:
Alex Hinman, BA, CCRP
Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Telephone: 414-805-9001
Fax: 414-805-9025

MCW Sub-investigator (Nurse Teacher)
Jayme Cotter MS, RN, ACNS-BC, AOCNS
Froedtert & Medical College of Wisconsin
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: 414-805-0966
Fax: 414-805-9995
Email: jayme.cotter@froedtert.com

DSMC Coordinator:
Jennifer Bollmer, PhD
Protocol Review and Monitoring System (PRMS) Coordinator
Medical College of Wisconsin
Cancer Center Clinical Trials Office (CTO)
9200 W. Wisconsin Ave.
Milwaukee, WI 53226
Phone: (414) 805-1947
Fax: (414) 805-8282
Email: jbollmer@mcw.edu

MCW Multisite Team Email:
OutpatientTrial@mcw.edu

VERSION HISTORY

Version	Date
1	07-12-2019
2	11-08-2019
3	04-15-2020

TABLE OF CONTENTS

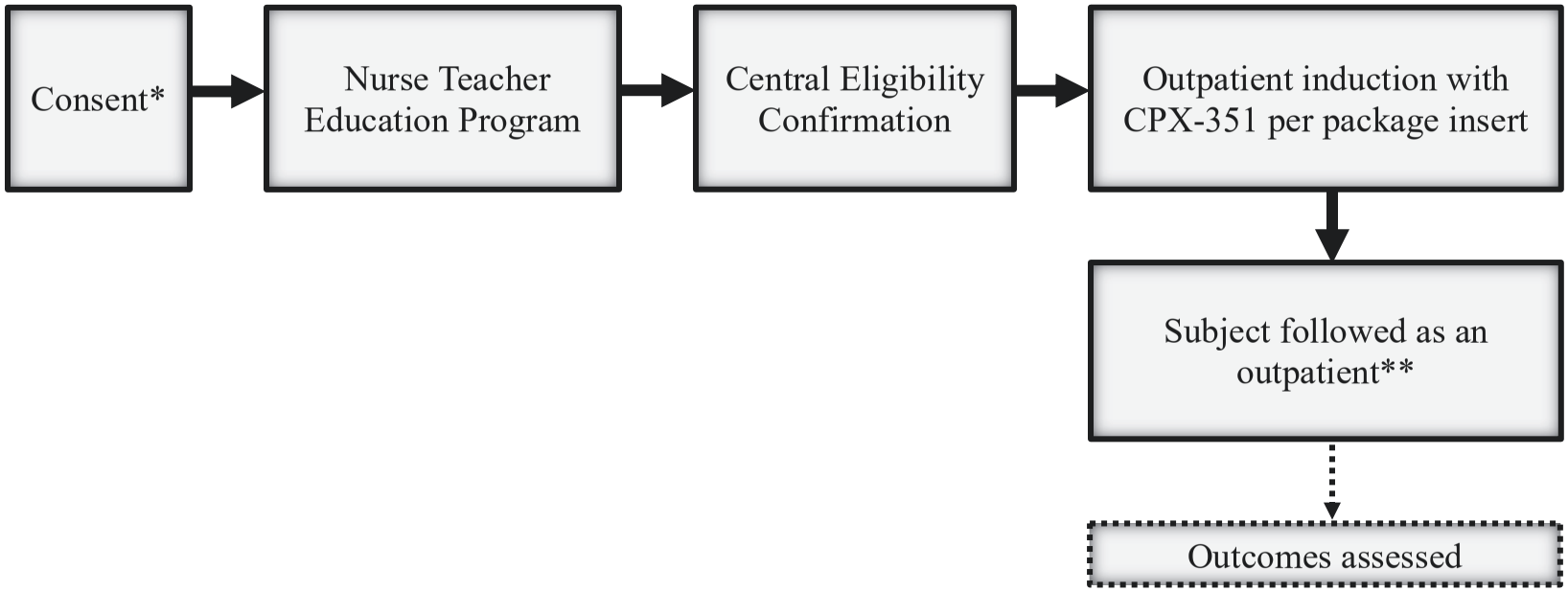
PROTOCOL SUMMARY

Title	A multi-institutional, phase IV project to study the feasibility of safely managing patients receiving induction with liposomal daunorubicin and cytarabine (CPX-351) for acute myeloid leukemia (AML) in an outpatient environment
Sponsor	Laura C. Michaelis, MD (Medical College of Wisconsin)
Principal Investigator	Laura C. Michaelis, MD
Clinical Trial Phase	Phase IV
Study Population	Adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)
Primary Aim	To estimate the feasibility of an outpatient care model for induction and management of patients with AML who receive induction therapy with liposomal daunorubicin and cytarabine (CPX-351).
Secondary Aims	1. To estimate the overall inpatient time for subjects who receive CPX-351 induction as an outpatient. 2. To estimate the incidence of admission to an intensive care unit in subjects treated in an outpatient environment. 3. To estimate the incidence of 30-day all-cause mortality in subjects treated in an outpatient model 4. To estimate the incidence of 60-day all-cause mortality in subjects treated in an outpatient model. 5. To describe the health care resource utilization for subjects induced with an outpatient care model. 6. To assess the health-related quality of life, anxiety levels and treatment-related worry for subjects receiving induction chemotherapy in an outpatient environment immediately prior to induction, 7–10 days following induction and 30 and 60 days after induction. 7. To assess the health-related quality of life anxiety levels and treatment-related worry for the primary caregiver of subjects receiving induction chemotherapy in an outpatient environment immediately prior to induction, 7–10 days following induction and 30 and 60 days after induction.

Study Design	Single-arm, multicenter run-in phase (six subjects), multicenter continuation phase (114 subjects), Phase IV study.
Intervention Description	CPX-351 is administered, according to FDA approval, to subjects who meet medical and logistical criteria for study enrollment. The study intervention is the application of a prescribed outpatient care model, including a nurse teacher educational program and quality of life surveys for both subjects and caregivers. Induction therapy and medical follow up are performed without prophylactic admission to an inpatient facility.
Number of Subjects	120 subjects (6 for run-in phase, 114 for continuation phase)
Subject Participation Duration	60 days
Estimated Time to Complete Enrollment:	24 months

STUDY SCHEMA

Run-In Phase: Six subjects, enrolled according to monitoring/stopping rules (refer to section 9.4).
Continuation Phase: After DSMC safety assessment of the run-in phase, the DSMC approves or denies continued enrollment of 114 subjects in the multi-institution continuation phase.



* Both subject and caregiver undergo the consent process. Each site implements a study-specific Nurse Teacher Education Program for all consenting subjects and caregivers. Quality of life surveys are obtained from the subject and primary caregiver at baseline, days 7–10, day 30, day 60 (+/- 5 days).

** Prespecified pattern of monitoring applied (refer to Study Calendar of Events). Subjects are admitted/readmitted according to section 5.

STUDY CALENDAR OF EVENTS

Procedure	Screening[1] (-7 days)	Induction Therapy						Thrice Weekly Until Count Recovery [9]	Once Weekly Until Count Recovery[9]	Day 30, Day 60 (from Day 1) ± 5 Days	Follow Up[6] (Day 90 ± 5 days)
		Day 1 [13]	Day 2	Day 3	Day 4	Day 5	Day 6				
Informed consent	X										
Survival status											X
Medical/Leukemia History	X										
Physical Exam: MD or APP	X	X		X		X			X	X	X
Oncology Nurse Assessment (in clinic)							X	X			
Oncology Nurse Assessment (phone call to subject) [5]			X		X			See footnote 5			
Vitals Signs (in clinic)	X	X		X		X	X	X		X	X
ECOG Status or Karnofsky Performance Status	X									X	X
Hematology[7]	X	X		X		X		X			
Comprehensive Metabolic Panel (CMP) [7]	X	X		X		X	X	X			
Urinalysis	X										
Pregnancy test (serum or urine) [12]	X										
Bone Marrow Biopsy and/or Aspirate and/or pathologic confirmation of AML (meeting eligibility criteria) from peripheral blood smear	X										
Echocardiogram or MUGA	X										
Hospitalization Tracking[2]		Day 1 through end of treatment[10]									X[2]

Procedure	Screening[1] (-7 days)	Induction Therapy						Thrice Weekly Until Count Recovery[9]	Once Weekly Until Count Recovery[9]	Day 30, Day 60 (from Day 1) ± 5 Days	Follow Up[6] (Day 90 ± 5 days)
		Day 1[13]	Day 2	Day 3	Day 4	Day 5	Day 6				
Transfusion Tracking[3]		Day 1 through end of treatment[10]									
Intravenous Antimicrobial Therapy and Growth Factor Tracking[4]		Day 1 through end of treatment[10]									
Cytogenetics	X										
Adverse Events	X	X		X		X	X	X	X	X	
Concomitant Medications	X								X	X	
Prophylactics: Antimicrobials	X										
Tumor Lysis prophylaxis	X										
QOL Surveys: Subject and Caregiver		X						Once between day 7-10		Day 30 (± 5 days) and Day 60 (± 5 days)	
Central Eligibility Confirmation	X										
Nurse Teacher Education Program	X										
Study Diary[8]		Day 1 through end of treatment[10]									
Drug Administration											
Liposomal daunorubicin/cytarabine (CPX-351)[11]		X		X		X					

[1] Screening procedures must be performed within seven days of enrollment (central eligibility confirmation). Bone marrow biopsy and/or aspirate, and ECHO/MUGA may be performed within 14 days of enrollment (central eligibility confirmation). Time from enrollment to start of treatment should be no more than seven days.

[2] Collect data on hospitalizations for data entry, including: date and time of admission and discharge from inpatient hospital, date and time of admission and discharge to intensive care unit, date and time of admission and discharge from skilled nursing facilities, date and number of unscheduled physician/APP office visits, dates and number of emergency room visits and any physician recommendations to the subject that they be admitted to the hospital or be assessed in an emergency room. The following information should be collected for each admission event: first collected vital sign readings at initial point of care (i.e., emergency room, floor bed), whether the admission was to a floor bed or ICU bed, the documented reason for admission, if vasopressor therapy was required during hospitalization with the date and time started and completed, and if intubation was required during hospitalization with the date and time started and completed. This data collection should also occur on the day 60 follow up visit.

[3] Collect data on transfusions for data entry, including: date and quantity of red blood cell units and platelet units.

[4] Collect data on use of IV antimicrobial therapy, including name, date administered. Collect data on use of granulocyte-stimulating factors and erythrocyte stimulating agents, including name and date administered.

[5] Oncology nurse contacts the subject by phone twice weekly (M-F), on days when subject does not have a clinic visit scheduled and is not admitted to the hospital. This should continue until count recovery or day 60 (post first dose of CPX-351), whichever comes first. The nurse should review the study diary and symptoms over the phone and query any concerning symptoms/events that could impact subject safety.

[6] Follow-up phase occurs from day 60 post first dose of CPX-351 to day 90 post first dose of CPX-351.

[7] CBC with manual differential. Chemistries: BMP, LFTs, phosphorus, uric acid, LDH, creatinine and calcium.

[8] Refer to appendix 5 for study diary template

[9] Preferably Monday, Wednesday, Friday or Tuesday, Thursday, Saturday. If not, consecutive days are not counted (e.g., Monday, Tuesday, Friday counts as two draws). These lab tests, and the timing of the tests, are required at a minimum. Treating physicians may obtain additional standard of care lab tests, per their discretion. Refer to section 5 regarding the treatment plan. Count recovery for the purposes of this study is defined as ANC >500 *and* two consecutive instances of platelet counts above the level of 50,000/uL (without the need for platelet transfusions). These procedures occur until count recovery or day 60, whichever comes first.

[10] End of treatment (EOT) is defined as count recovery or day 60, whichever comes first.

[11] If the subject receives reinduction with CPX-351 therapy, they may remain on study until EOT (i.e., count recovery or day 60, whichever comes first). However, once admitted after reinduction therapy, subjects may not be discharged unless they are removed from the study.

[12] For women of childbearing potential (refer to eligibility criteria), a negative pregnancy test must be obtained prior to enrollment and within seven days prior to the first dose of CPX-351, then as clinically indicated.

[13] Day 1 procedures in the study calendar of events occur prior to first dose. If they were performed within 24 hours of first dose as part of screening procedures, they do not need to be repeated, unless clinically indicated. Labs on day 1 must meet eligibility criteria to continue day 1 treatment.

List of Abbreviations

ADCR	Associate Director for Clinical Research
AE	Adverse Event
ALL	Acute Lymphocytic Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
AML-MRC	Acute Myeloid Leukemia with Myelodysplasia-Related Changes
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BMP	Basic Metabolic Panel
BUN	Blood Urea Nitrogen
CAP	Corrective Action Plan
CAT	Computer Adaptive Testing
CBC	Complete Blood Cell (Count)
CCCTO	Cancer Center Clinical Trials Office
CITI	Collaborative Institutional Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CPRs	Continuing Progress Reports
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DLT	Dose-Limiting Toxicity
DOA	Delegation of Authority
DOT	Disease-Oriented Team
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic Medical Record
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
LFT	Liver Function Tests
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MCW	Medical College of Wisconsin

MCWCC	Medical College of Wisconsin Cancer Center
MDS	Myelodysplastic Syndromes
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
ORR	Overall Response Rate
PD	Disease Progression
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-reported Outcome
PRO-CTCAE	Patient Reported Outcomes-Common Terminology Criteria for Adverse Events
QA	Quality Assurance
QOL	Quality of Life
RBC	Red Blood Cell (Count)
SAE	Serious Adverse Event
SD	Stable Disease
sIRB	Single Institutional Review Board
SOP	Standard Operating Procedure
SOTD	Successful Outpatient Treatment Delivery
SRC	Scientific Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
t-AML	Therapy-related Acute Myeloid Leukemia
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
WBC	White Blood Cell (count)

1 BACKGROUND AND RATIONALE

Background

Otherwise fit adults with acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS) may achieve cure with intensive induction or reinduction (salvage) chemotherapy. Traditionally, care is provided in an inpatient environment, a model developed in the early days of treating children with acute lymphocytic leukemia (ALL) with multi-agent induction therapy and used in adults due to the need for frequent transfusions and the risks for treatment-related mortality from sepsis. [1,2] Accordingly, most subjects who get induction therapy for AML receive this therapy as inpatients and are typically discharged only after neutrophil recovery. The result is that the vast majority of subjects receiving cytotoxic induction or reinduction therapy will be hospitalized for between three to five weeks. Subjects who have relapsed and receive a salvage therapy for reinduction are often hospitalized are treated under a similar practice pattern. [3]

In the last decade, there has been increasing interest in alternatives to care delivery models in hematologic malignancies. [4,5,6] For example, there have been published studies about the safety of autologous and allogeneic stem-cell transplants performed in a largely outpatient setting. [7,8] Improvements in supportive care, especially effective, prophylactic oral antimicrobials, have led to a substantial reduction in the risk for infection during induction. Similarly, the ability to administer red blood cell and platelet transfusions in the outpatient setting has increased. [9,10] While not robust, there is some literature supporting the psychological and economic benefits of outpatient treatment. [11] In fact, several cost analyses have shown that the prolonged inpatient stays are a key driver of the exceedingly high costs of leukemia care. [12-15] Routinely, chemotherapy regimens of similar intensity are used for AML consolidation therapy and many subjects are discharged for follow-up as outpatients.

One large, single-institution pilot study has been published on the feasibility and safety of an early discharge model of care for a select group of subjects after completion of intensive induction therapy for AML or MDS. [16-18] The results of a pilot study were published in 2015. In this study, Dr. Roland Walter and colleagues enrolled 178 AML subjects in a clinical trial of early discharge after induction therapy. Investigators had predesignated medical and social/logistical criteria in order to participate in the early discharge program. Of the 178 subjects, all met medical criteria for discharge, but only 107 met both medical and logistical criteria. The remaining 29 served as inpatient controls. Researchers found that the early discharge was feasible and appeared to result in a decrease in resource utilization without significant impact on subject safety.

Liposomal Daunorubicin and Cytarabine (CPX-351)

In the last year, new data has led to the approval of a novel induction regimen for AML: a liposomal formulation of daunorubicin and cytarabine. Unlike the traditional regimen of 7+3 (daunorubicin administered by bolus IV on days 1,2 and 3 and cytarabine administered as a 24-hour continuous infusion over days 1–7), CPX-351 is administered on days 1, 3 and 5 via intravenous infusion over 90 minutes and on days 1 and 3 for subsequent cycles of induction, if needed. This agent is approved for subjects with newly diagnosed AML with myelodysplastic-related changes or that is secondary to prior chemotherapy. With the advent of this formulation, subjects being induced may not need to be hospitalized merely for the 24-hour infusion of cytarabine, as had been the case in the past.

Among the most notable findings of the early studies of CPX-351 has been the relative mitigation of traditional toxicities seen with 7+3, presumably because of the liposomal formulation. Conventional drug administration can lead to changing drug ratios after dosing, thus, preventing the maintenance of any

particular drug ratio that could potentially optimize antitumor activity. However, the development of CPX-351 was based on the hypothesis that liposomal drug delivery allows for fixed molar ratios and increased antileukemia efficacy. In the phase II randomized study of CPX-351 (CPX-351) vs. traditional induction in older subjects, recovery from cytopenias was slower after CPX-351 (median days to absolute neutrophil count ≥1000: 36 vs. 32; platelets >100 000: 37 vs. 28) with more grade 3–4 infections but without increase in infection-related deaths (3.5% vs. 7.3%) or 60-day mortality (4.7% vs. 14.6%). [19] In this study, three of the 85 subjects treated with CPX-351 died by day 30, and by day 60 only one additional subject had died. Grade 5 toxicities on the investigational arm included one death from pneumonia, and three deaths from sepsis out of 85 subjects treated. Among the 85 subjects who received CPX-351, there were 54% incidents of febrile neutropenia, 30 incidents of bacteremia, 10 incidents of sepsis and 12 recorded incidents of fungal infection. For all subjects on study, there was a trend to a decrease in induction mortality.

The results of the Phase III study performed in adults between the age of 60 to 75 years were published in 2018. These data show subjects getting CPX-351 had a 5.9% 30-day mortality rate while subjects getting 7+3 had a 10.6% rate of death in that same time period. In the first 60 days after induction, 13.7% subjects getting CPX-351 had died, 3.3% of which were due to progressive disease, and 10.4% were due to treatment-related mortality. [20]

Rationale

With the approval of CPX-351 therapy for subjects with secondary or treatment-related AML, one can devise a treatment strategy for a subject that begins in an outpatient setting and continues in that setting as long as subjects can avoid toxicities that require hospitalization, for instance, febrile neutropenia. In fact, a retrospective review of consolidation administration, presented at the 2017 ASCO meeting, demonstrated that at experienced centers, outpatient consolidation did not worsen outcome. [21] Studying the feasibility of this approach in induction can provide information on its safety, the consequences on resource utilization and also an opportunity to understand, in a more rigorous way, the impact of outpatient induction strategy on the health-related quality of life of the subjects and their caregivers.

It is on the basis of this background that we hypothesize that it is feasible, under strict medical and logistical conditions, for a select group of hospitals to safely utilize an outpatient clinical environment to deliver CPX-351 as induction chemotherapy to adult subjects with treatment-related AML or AML with myelodysplastic-related changes. Successful outpatient treatment delivery might alter or improve health-related quality of life for the subject or caregiver. Benefits of such a shift from inpatient to outpatient care could also substantially decrease hospital costs, and reduce the incidence of nosocomial infections, a primary concern and contributor to death among these subjects.

The main objective of this multicenter study is to test the feasibility of utilizing, among participating academic medical centers, a set of medical and logistical criteria for treating eligible subjects with AML in an outpatient or early discharge model. Successful outpatient treatment delivery would be defined as feasible if more than 70% of screened and eligible subjects are able to adhere to protocol-defined appointments and readmission recommendations. This study would allow us to estimate whether there are safety concerns with such a model, as defined by 30-day, 60-day mortality, the likelihood of hospital admission, the likelihood of admission to an intensive care unit and describe the character of toxicities. In addition, this study will allow us to measure the quality of life in both subjects and caregivers and pilot a uniform teaching module to prepare subjects and caregivers for successful outpatient induction delivery.

2 AIM AND ENDPOINTS

We hypothesize that it is feasible, given careful subject selection and given appropriate outpatient clinical resources, to deliver outpatient induction chemotherapy with CPX-351 to adult subjects with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

2.1 Primary Aim

1. To estimate the feasibility of an outpatient care model for induction and management of subjects with AML who receive induction therapy with liposomal daunorubicin and cytarabine (CPX-351).

2.2 Secondary Aims

1. To estimate the overall inpatient time for subjects who receive CPX-351 induction as an outpatient.
2. To estimate the incidence of admission to an intensive care unit in subjects treated in an outpatient environment.
3. To estimate the incidence of 30-day all-cause mortality in subjects treated in an outpatient model.
4. To estimate the incidence of 60-day all-cause mortality in subjects treated in an outpatient model.
5. To describe the healthcare resource utilization for subject induced as outpatients.
6. To assess the quality of life, anxiety levels and health care priorities for subjects receiving induction chemotherapy in an outpatient environment at the time of induction, between days 7–10, 30 and 60 days following induction.
7. To assess the quality of life anxiety levels and health care priorities for the primary caregiver of subjects receiving induction chemotherapy in an outpatient environment at the time of induction, between days 7–10, 30 and 60 days following induction.

2.3 Primary Endpoints

The primary endpoint of this study is feasibility. If the primary endpoint is met, we consider that to be successful outpatient treatment delivery (SOTD).

The primary endpoint will be met if more than 70% of screened and eligible subjects are able to:

1. Between enrollment and end of treatment (count recovery or day 60, whichever comes first) **both**
   a) Adhere to outpatient follow-up appointments. Adherence is defined as missing no more than 5% of protocol-mandated outpatient visits (except for reasons of hospitalization).
   b) Adhere to readmission recommendations. Adherence is defined as 100% compliance with medical provider recommendations to be admitted to the hospital (except for reasons of adopting a palliative or hospice approach to care).

The study has stopping rules (refer to section 9.4) to pause and proceed with a DSMC safety evaluation if there is sufficient evidence indicating that the 30-day mortality exceeds 6% or the 60-day mortality exceeds 14%.

2.4 Secondary Endpoints

1. Estimate the overall inpatient time for subjects who receive CPX-351 induction as an outpatient.
    a. "Inpatient time" will be defined as the days spent hospitalized in an inpatient environment between day 1 of induction and day 60 following induction. A day is defined by 1 midnight spent in a hospital.
2. Estimate the incidence of admission to an intensive care unit between the time of induction and day 60.
3. Describe the reasons for admission to the hospital for subjects who undergo outpatient induction therapy.
    a. Admission defined as being admitted over one midnight to a hospital between induction and day 60.
4. Estimate the incidence of 30-day and 60-day mortality.
    a. 30-day mortality defined as death within 30 days of induction.
    b. 60-day mortality defined as death within 60 days of induction.
5. Describe resource utilization for subjects induced as outpatients, including
    a. Number of inpatient days between day 1 of induction and day 60 following induction.
    b. Number of days in ICU between day 1 of induction and day 60 following induction.
    c. Number of outpatient physician visits between day 1 of induction and day 60 following induction.
    d. Number of outpatient clinic visits between day 1 of induction and day 60 following induction.
    e. Number of units of RBCs between day 1 of induction and day 60 following induction.
    f. Number of platelet transfusions between day 1 of induction and day 60 following induction.
    g. Number of subjects with documented blood stream infections between day 1 of induction and day 60 following induction.
    h. Number of subjects with documented infections of C difficile between day 1 of induction and day 60 following induction.
    i. Number of days with IV antibiotic usage between day 1 of induction and day 60 following induction.
    j. Number of doses of granulocyte-stimulating factor, erythropoietin administered between day 1 of induction and day 60 following induction.
6. Describe the health-related quality of life and treatment-related worry for subjects, including
    a. PROMIS Fatigue
    b. PROMIS Anxiety
    c. PROMIS Depression
    d. PROMIS Sleep Disturbance
    e. PROMIS Ability to Participate in Social Roles and Activities
    f. PROMIS Physical Function
    g. PROMIS Social Support (Instrumental)
    h. PRO-CTCAE symptoms
    i. Outpatient treatment worries and burden of subjects with AML
7. Describe the same health-related quality of life and treatment-related worry for the primary caregiver of subjects, including
    a. PROMIS Fatigue
    b. PROMIS Anxiety
    c. PROMIS Depression
    d. PROMIS Sleep Disturbance
    e. PROMIS Ability to Participate in Social Roles and Activities
    f. PROMIS Physical Function

g. PROMIS Social Support (Instrumental, Emotional)
h. Outpatient treatment worries of caregivers of subjects with AML

3 STUDY DESIGN

3.1 General Description

This is a nonrandomized, single-arm, Phase IV study of the feasibility of an outpatient induction and management strategy for subjects with treatment-related acute myeloid leukemia or AML with myelodysplastic-related changes who receive induction therapy with CPX-351.

The trial will begin with a run-in phase. After six subjects are treated, their clinical outcomes will be assessed by the Data and Safety Monitoring Committee (DSMC). If no significant safety concerns are discovered, the protocol will then open to the continuation phase. A total of 120 subjects will be enrolled over approximately 24 months.

3.2 Design of Current Study

In this study, subjects who are eligible for treatment with CPX-351, according to the FDA approval, are reviewed for medical and logistical eligibility criteria. Subjects, and their caregivers, undergo a nurse teacher education program to familiarize them with an outpatient care model, including expectations for home care and for contacting their physician.

After central eligibility confirmation by MCW, subjects then receive induction as an outpatient, managed with transfusions and lab draws as an outpatient. Subjects will be hospitalized for care if they meet outlined criteria or if admission is deemed clinically necessary by their physician.

The study is aimed at understanding if it is feasible to administer CPX-351 as an outpatient induction medication. This study also measures the safety of this strategy by describing the clinical outcomes of this group of subjects, including the incidence and reasons for admissions and readmissions, the incidence of infections, the time of hospitalization, the time spent by subjects in an intensive care unit. Several other secondary endpoints will be examined, such as the subject's perceptions of outpatient care, the caregiver's perceptions of outpatient care, and a description of resource utilization.

4 OPERATIONAL CRITERIA

4.1 sIRB Requirements

The MCW sIRB is the IRB of record for all participating sites. All sites must follow MCW sIRB requirements and policies regarding subject participation, found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

4.2 Subject Status

Subject OnCore® (the study's data capture system) statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial, or study staff considering subject for the trial per institutional recruitment methods).
- Consented: consented, prior to eligibility confirmation.
- Screening: period after consent, but prior to central eligibility confirmation.
- Eligible: the local investigator confirms all eligibility criteria apply *and* the MCW principal investigator or MCW sub-investigator confirms central eligibility.
- On study/enrolled: date central eligibility is confirmed by the MCW principal investigator or MCW sub-investigator.
- On arm: date of enrollment.
- On treatment: first day that treatment was given until day 60.
- Off treatment: day 60 visit.
- On follow-up: immediately following day 60 visit until day 90 visit.
- Off study: follow-up period completed, with no additional data gathered.
- Off arm: same date as 'off-study' - follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local principal investigator (refer to section 4.10).

4.3 Prescreening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as subjects who were considered to participate in the clinical trial (with or without consent) but are not subsequently assigned to the study intervention or enrolled in the study.

Prescreening logs are maintained at each site, as follows:

- The templated log is preferred, but sites may use their own logs, if they track the number of subjects examined (prescreened) for trial participation and the reason for screen failure.
- Sites should maintain an identified log (never sent to MCW) that correlates with a coded deidentified log (sent to MCW).
- Participating sites must follow all HIPPA and sIRB requirements for disclosure of this information to MCW.
- Sites must report the log to the Multisite Coordinator (via. the Multisite Team Email) upon request (e.g., regular intervals and/or at remote monitoring visit calls).

4.4 Consent and Training

4.4.1 Nurse Teacher Education Program

A nurse teacher is defined as follows:

- An oncology certified nurse (at a minimum)
- Completed the study-specific training for the study-specific program (each nurse teacher will be provided the opportunity to ask questions with the MCW nurse teacher, if necessary)

A critical part of this study is subject education and subject symptom diary/record-keeping. MCW study staff will provide a uniform, study-specific training to local nurse teachers, in order to provide the minimal acceptable education to the subject and caregiver for outpatient management. Note, there may be more than one nurse teacher at a participating site.

Sites must *at a minimum* use the nurse teacher education program presentation provided for education, though they can provide additional information as part of education per their institutional guidelines.

Sites perform the study-dictated nurse teacher education program in the following manner:

- The full program is only performed after consent.
- The nurse teacher should not skip or leave out any aspect of the full study-dictated presentation simply because an aspect had been reviewed during consent (i.e., the full training must occur regardless of what was discussed during consent).
    - The nurse teacher should provide each subject and caregiver detailed instructions on how to contact the local triaging physician/APP or covering physician 24 hours a day, seven days a week
    - Each site's educational program should provide local information on where the subject is to have laboratory tests and evaluations performed.
- Any standard-of-care training that occurs prior to consent will not be considered a deviation, though it should be documented in the subject's medical record.
- Completion of the subject and caregiver study-specific nurse teacher program with the nurse teacher and delivery of the required study-specific hand-out materials must be documented in the subject's electronic record (including completion of the diary antimicrobial sections)
- More than one caregiver may attend, however, only one primary caregiver will sign consent and must complete the nurse teacher education program.
- The nurse teacher must assess and confirm that she/he believes the subject and caregiver obtain a reasonable level of competency of the study-specific program and are equipped for managing the subject at home (i.e., they own or have access to a thermometer, understand instructions about calling, etc.). Refer to logistical eligibility criteria documentation requirements.
    - Please see appendix 4 for the subject/caregiver verification guide, to assist the nurse teacher in verification (may be used as source verification for eligibility).
    - If the nurse teacher identifies a significant deficiency in competency, the subject or caregiver may be re-educated until proficiency is obtained.
- If the nurse teacher does not attest that the subject or caregiver is considered safe for outpatient management, the subject will fail eligibility and will not be on study. This must be documented in the subject's electronic record and the reason recorded in the case report forms.

4.4.2 Subject and Caregiver Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians and/or other sIRB-approved recruitment methods.

It is recommended that research staff attempt to consent the subject and caregiver separately to avoid potential coercion. If unable to do so, the subject and caregiver may still be eligible for participation.

A signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and caregiver, with a copy filed in the medical record (per sIRB policies and institutional SOPs). The original will be kept on file with the study records.

After consent, the following occurs:

- A new subject entry into OnCore® must occur within 24 hours of consent.

- A case/subject/sequence number is assigned in OnCore® from the site in sequence (i.e., inputted from the site staff, not generated by OnCore®).
    - Sites enter the case number according to the following template "Site-VYX-001-X", where "Site" is an abbreviation of the site name (e.g., MCW), VYX indicates the trial, "001" is the sequential subjects who consented to the trial at the site (e.g., the first consented subject at MCW would MCW-VYX-001-P), and "X" is either "P" for subject or "C" for primary caregiver (NOTE: this applies only for the PROs and general tracking, but caregivers are listed in OnCore within the subject enrollment).

4.4.3 Study Diaries

Subject diary completion is as follows:

- The nurse teacher provides each subject a study diary (refer to appendix 5).
- Subjects keep daily logs of symptoms they are experiencing, as well as their temperature readings twice daily.
- Subjects record their daily doses of oral antimicrobial therapy (nurse teacher should review and complete those sections)
- During protocol-mandated visits and follow-up calls, nurses should review that subjects are appropriately taking all medications (particularly prophylactic antibiotics), temperature logs and any side effects.
- Subjects continue to complete the diary until count recovery or day 60, whichever comes first.

4.4.4 Ongoing Consent Process and Education

Treating physicians should continue to evaluate subject competency of the outpatient monitoring plan and study requirements throughout the trial. If any deficiency is noticed, the subject or caregiver may be reeducated until proficiency is obtained. If proficiency cannot be obtained, the nurse teacher must discuss it with the enrolling physician and if necessary, remove the subject from study intervention (see section 6 for expedited reporting requirements). This must be documented in the subject's electronic record and the reason recorded in the case report forms.

4.5 Screening Procedures

Refer to the study calendar of events.

The subject may be consented to the study if admitted to the hospital. The nurse teacher education program may occur while the subject is an inpatient, as long as the nurse teacher, caregiver, etc., are the same as would occur in an outpatient setting. If the subject is enrolled while inpatient, the site may administer the first dose inpatient and then discharge the subject as otherwise anticipated.

Screening assessments must be performed within seven days prior to central eligibility confirmation.

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the allowed window. Bone marrow biopsy and ECHO/MUGA (considered standard of care prior to CPX-351) may be performed up to 14 days before central eligibility confirmation.

4.6 Central Eligibility Confirmation

Central eligibility confirmation occurs in the following manner:

- Participating sites prepare eligibility documents.
    - The local PI or designated sub-investigator must review and sign/date the eligibility criteria section.
        - Confirmation may occur via email if a physical signature would significantly delay enrollment (sites should provide documentation of this potential delay with the eligibility supporting documents).
    - It is highly recommended that participating sites include written dates and/or values of procedures next to all criteria on the right margin of the page (e.g., ECOG score = 0 on date MM/DD/YYYY). The multisite coordinator may provide a completed example.
    - Subject initials and study case/sequence number should be written on each page of the eligibility pages and supporting source documents. All of which must be deidentified.
    - Supporting deidentified source documents are required for *all* items of eligibility criteria (i.e., age, nurse teacher documentation, etc.), consent and documentation of consent process (with key information circled, if possible, to aid in auditing and quick central eligibility confirmation).

- Central Eligibility Confirmation
    - The eligibility documents above are uploaded into Box.com (site folder access shared by the MCW multisite coordinator), and sites notify the multisite coordinator (via the MCW Multisite Team email) and MCW principal investigator via email of completion. Participating site staff must inform the MCW principal investigator if the multisite coordinator returns an out-of-office email reply. If sites have an issue uploading into Box.com, emailed documents will suffice until the issue is resolved.

    - The MCW principal investigator or MCW sub-investigator (with the assistance of the multisite coordinator) will review, request additional information and confirm (via signature or email confirmation if a physical signature would significantly delay enrollment) subject eligibility within approximately one business day of receipt of documents and email notice. (*Monday-Friday, excluding holidays. Sites must email MCW principal investigator and multisite coordinator prior to a Friday enrollment or holiday.*)

- **Eligibility criteria within a time frame of "enrollment" mean central eligibility confirmation from MCW (not the local investigator). Sites must ensure the one business day window for central confirmation does not put an eligibility procedure outside of the required time window. If this is potentially an issue, sites should notify the Multisite Coordinator (via. the Multisite Team Email) and MCW principal investigator with supporting documents prior to intended enrollment date.**

*Note (for MCW only): It is preferred that MCW staff provide the Multisite Team central eligibility documents for their review and clarification/documentation requests prior to MCW investigator signoff, but MCW subjects are considered enrolled at time of MCW study principal investigator or MCW sub-investigator eligibility confirmation. Source document uploading is not required for MCW.

Enrolling investigator signature/date _____

4.7 Eligibility Criteria

No waivers of protocol eligibility will be granted, but when clinical factors relating to an eligibility item are unclear or questionable, the MCW PI can only provide guidance or clarification on eligibility.

Medical Inclusion Criteria

1. Subjects with newly diagnosed acute myeloid leukemia who are eligible for treatment with CPX-351 therapy according to the FDA approval and indication: therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
2. Age ≥ 18 years
3. ECOG of 0 or 1 (or Karnofsky Performance Status equivalent of 70 or above).
4. Total bilirubin ≤ 3 mg/dL.
5. Creatinine clearance > 30mL/min by Cockcroft/Gault equation.
6. Adequate cardiac function (ejection fraction ≥ 50%) for anthracycline therapy, assessed by ejection fraction via MUGA or echocardiogram.
7. Total WBC of ≤ 20,000/uL on peripheral blood assessment (hydrea and/or leukapheresis allowed).
8. No evidence of active, uncontrolled infection.
9. No evidence of clinically significant disseminated intervascular coagulation
10. No clinically significant abnormalities in core vital signs like heart rate, blood pressure or oxygenation which require inpatient evaluation or monitoring.
11. In the opinion of the enrolling physician, the subject is not at risk for clinically significant tumor lysis syndrome based on clinical assessment, CBC (complete blood count), CMP (comprehensive metabolic panel), uric acid, and LDH.
12. In the opinion of the enrolling physician, no medical conditions that preclude the subject or the primary caregiver from transportation to and from the outpatient clinical care facility.
13. Both subject and the identified primary caregiver(s) signed informed consent.
14. In the opinion of the enrolling physician, there are no medical contraindications to outpatient induction and management.
15. Male subjects, even if surgically sterilized (i.e., status post vasectomy), must agree to one of the followings:
    - Practice effective barrier contraception during the entire study period and through 90 days after the last dose of CPX-351,
      OR
    - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

    Female subjects must meet one of the followings:
    - Postmenopausal for at least one year before enrollment,
      OR

Enrolling investigator signature/date _____

- Surgically sterile (i.e., undergone a hysterectomy or bilateral oophorectomy),
  OR
- If the subject is of childbearing potential (defined as not satisfying either of the above two criteria), she must agree to practice two acceptable methods of contraception (combination methods require use of two of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male or female condom, hormonal contraceptive) from the time of signing of the informed consent form through 90 days after the last dose of CPX-351, **OR**
  - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable contraception methods.)

Logistical Inclusion Criteria

1. The subject must be able to reside within approximately 45 minutes of the hospital where induction therapy is administered, during normal driving conditions (in the opinion of the enrolling physician), until count recovery or 60 days post-treatment, whichever comes first
2. The enrolling physician must verify and attest that the subject has a primary caregiver meeting all the following criteria:
   2.1 Reside with the subject.
   2.2 Be able to care for the subject full time or arrange to share full-time care with secondary caregivers.
   2.3 Provide transportation.
   2.4 Respond to clinical issues that arise.
   2.5 Communicate with subject and physician in a timely manner.
   2.6 Age $\geq$ 18 years
3. The nurse teacher must verify that the subject and primary caregiver have completed and adequately understand the study-dictated nurse teacher educational program.
4. The nurse teacher must verify the subject and primary caregiver have capacity to comply with outpatient management program.
5. The subject must have reliable, working telephone access.
6. The subject must be willing and able to attend all protocol-dictated visits and be seen frequently as an outpatient at the clinical care facility where induction therapy is administered.

Exclusion Criteria

1. Pregnant women (per pregnancy test in women of childbearing potential) or women who are breast-feeding.
2. Subjects currently receiving any investigational agents.
3. Subjects must not have current evidence of another malignancy that requires treatment.
4. Subjects diagnosed with Wilson's disease and/or copper-related metabolic disorders.

"I have reviewed all inclusion/exclusion criteria and confirm the subject is eligible."	
Enrolling Investigator Name (print)	
Enrolling Investigator Signature	**Date**

"This subject is eligible for the study and considered on study/enrolled."	
MCW Study PI Name (printed) *or MCW Designee	
MCW Study PI Signature *or MCW Designee	**Date**

4.8 Enrollment

Subject enrollment logistics are defined as follows:

- OnCore® enrollment entry (on study status) must occur within 24 hours of central eligibility confirmation (i.e., date the MCW principal investigator or MCW sub-investigator confirmed enrollment), unless specified otherwise (e.g., when nearing accrual goal)
- The subject case/sequence number is the same throughout the trial.

4.9 Treatment

Treatment must start within seven days of enrollment (i.e., central eligibility confirmation). If unforeseen issues occur and treatment is delayed after enrollment (i.e., in the opinion of the local investigator, a change from screening is significant enough to warrant the hold), the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email) must be emailed for MCW principal investigator approval to continue treatment outside the seven-day window. The MCW principal investigator will consider if any procedure for safety should be repeated, or if the subject should be discontinued from the trial.

Day 1 is defined as the first day that CPX-351 is given to the subject.

Day 1 procedures in the study calendar of events occur prior to the first dose. If they were performed within 24 hours of first dose as part of screening procedures, they do not need to be repeated unless clinically indicated. Labs on day 1 must meet eligibility criteria to continue day 1 treatment.

For women of childbearing potential, a negative pregnancy test must be obtained prior to enrollment and within seven days prior to the first dose of CPX-351, then as clinically indicated.

4.10 Discontinuation of Study Treatment/Intervention, Withdrawal and Compliance

Discontinuation of Treatment/Intervention

Standard-of-care *treatment* is considered delivery of CPX-351, while study *intervention* is considered study-dictated research procedures (e.g., outpatient setting, study calendar of events, nurse teacher education program, quality of life questionnaires, etc.).

Discontinuation from CPX-351 does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed, as indicated by the study protocol, and AEs/SAEs will continue to be reported, according to this protocol.

It is preferred that in cases of intended discontinuation from study intervention that are not due to adverse events or of immediate subject safety concern, participating sites are encouraged to email the Multisite Coordinator and MCW Study PI to determine if any efforts/actions might be safely taken to continue subject participation.

Refer to section 6 for expedited reporting requirements upon discontinuation of treatment/intervention.

Study intervention may continue until:

- Count recovery defined for the purposes of this study as ANC >500 *and* two consecutive instances of platelet counts above the level of 50,000/uL (without the need for platelet

transfusions).
- Disease progression, as defined by requiring salvage chemotherapy other than CPX-351. Subjects may stay on study for reinduction with CPX-351, but if readmitted to hospital will not be discharged for additional outpatient management.
- Subject receives consolidation therapy.
- Subject proceeds to stem-cell transplant.
- General or specific changes in the subject's condition renders the subject unacceptable for continuation on study in the investigator's judgment.
- Subject decides to withdraw from the study
- The subject has significant noncompliance such that the enrolling physician or MCW PI believe warrant discontinuation.
- The subject no longer meets logistical eligibility criteria.
- Study stopping rules are met (refer to section 9.4)
- Study discontinuation or closure (refer to section 4.14)

Subject or Caregiver Consent Withdrawal

A subject or caregiver may decide to withdraw from the study at any time.

If a subject intends on withdrawing consent, sites should confirm which of the following options the subject chooses, document the discussion, upload the documentation to Box.com and update OnCore®, and email the Multisite Coordinator (via. the Multisite Team Email):

- Full consent withdrawal, with no study follow-up.
- Selective consent withdrawal from interventional portion of the study, but agree to continued follow-up of associated clinical outcome information.

If a primary caregiver withdraws consent or can no longer provide care for the subject, in the absence of subject consent withdrawal, the treating physician and subject must evaluate if another caregiver is available that meets all protocol requirements. If so, the following occurs:

- Email notice to MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email) within 24 hours.
- Caregiver consent is obtained.
- Caregiver completes the nurse teacher education program.
- Nurse teacher verifies completion of nurse teacher education program and appropriate competency of the eligibility of caregiver.
- Documentation uploaded into Box.com.

If another eligible caregiver cannot be found, the following occurs:

- The subject should be admitted (if applicable given where the subject is in the course of treatment, per physician discretion).
- If the subject does not comply with the admission recommendation, refer to section 5.9.1.
- Data should continue to be obtained, recording the situation in OnCore®.

Investigator-Initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interest. Reasons for withdrawing a subject include, but are not limited to, disease progression, a subject's noncompliance, determination that the subject no longer meets logistical eligibility or simply

significant uncertainty on the part of the investigator that continued participation is prudent. Sites should notify the Multisite Coordinator (via. the Multisite Team Email) and MCW study principal investigator within 24 hours in such cases (refer to section 6). The reason for study withdrawal and the date the subject was removed from the study must be documented in medical record and recorded in OnCore®.

Subject and Caregiver Adherence

Pharmacy accountability logs for CPX-351 will measure compliance with study treatment dosing.

This protocol is testing whether an outpatient management program for induction therapy for AML is feasible and safe. Feasibility endpoints require documentation of subject adherence with study procedures.

Sites must document any and all events when subjects:

- Refuse treating physician's recommendation for admission.
- Miss protocol-mandated visits or nursing assessments (i.e., study calendar of events).
- Are unable to adhere to outpatient management recommendations.
- In the opinion of their treating physician, are no longer eligible based on logistical criteria.

This protocol also requires adequate and reliable caregivers for the subject. Sites must document any and all events when a primary caregiver:

- Refuses to, or is unable to, transport subject to protocol-mandated visits and/or is unable/unwilling to find a substitute
- Is unable to be reached when a subject attempted to contact the caregiver to perform caregiver duties.

"Significant noncompliance" is defined as any "significant deviation" (refer to section 5.7 and 6.10 for reporting requirements).

After any significant subject or primary caregiver noncompliance event, the following re-education action must occur:

- Discussion with treating physician regarding subject safety actions to be taken.
- Reeducation from nurse teacher on how to avoid further noncompliance.
- Report expedited according to section 6.5.
- If two of the same events occur, the enrolling physician and/or MCW PI may consider removing the subject from study intervention.

After any subject or caregiver noncompliance event that does not meet the "significant" criteria, the following should occur:

- Site staff document the occurrence.
- Report the event in OnCore®'s case report form

If a subject discontinues CPX-351 prior to the three induction doses, the treating physician must perform the following additional procedures:

- Ensure subject safety (e.g., admit the subject as necessary, provide supportive care, etc.).

- Document reason for discontinuation and email the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email) within 24 hours of discontinuation (refer to section 6 for reporting requirements).
- The treating physician may continue with other AML treatment, and seen according to that regimen's schedule, per his/her discretion.
- Perform the 30-day, 60-day follow-up procedures

Staff Compliance

While protocol deviations are related to the protocol, failure to follow any site-specific documents/SOPs/standard practice(s) that the protocol references may also be considered a deviation, including, but not limited to, the following:

- Nurse teacher education program

"Significant noncompliance" is defined as any "significant deviation" (refer to section 5.7 and 6.10).

After any significant staff noncompliance event, the following re-education action must occur:

- Reeducation focused on how to avoid further noncompliance, with applicable staff.
- Enact a corrective action plan, if necessary.
- Report expedited according to section 6.5.

4.11 Follow-Up and Lost to Follow-Up

The following actions must be taken if a subject fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the subject.
- A subject is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occur at two consecutive scheduled protocol calendar time points:
    - Three telephone calls (at least one day apart) from the study team are unanswered
      AND
    - A letter (see appendix 2 for template) to the subject's last known mailing address is not responded to within six business days of mailing.
      AND
    - These contact attempts must be documented in the subject's medical record or study file.
- Update OnCore® (Follow-up tab and eCRF) when a subject is officially considered lost to follow-up, and email the Multisite Coordinator (via. the Multisite Team Email) and MCW principal investigator.
- If a subject is considered lost to follow-up, but subsequently contacts the participating site study team, the subject should be considered in follow-up again, with subject approval, and the study team must notify the Multisite Coordinator (via. the Multisite Team Email).

4.12 Accrual Suspension and Closure

The multisite coordinator facilitates the suspension and closing of accrual in the following manner:

- Refer to section 9.4 regarding opening of continuation phase after completion of the run-in phase.

- The multisite coordinator sends accrual reports periodically and notifies sites when nearing suspension requirements (see below).
    - Sites must inform the Multisite Coordinator (via. the Multisite Team Email) of any new or potential consents by the end of the business day when a total of 100 subjects are enrolled from all participating sites.
- The multisite coordinator will inform participating sites when the actual or potential number of consents equals the number of available enrollment slots (e.g., 119 enrolled of the intended 120 accrual goal and another subject consents), at which time new consenting is suspended.
    - If one of the consented subjects (in screening) is ineligible, accrual reopens until a subject is consented to fill that accrual spot.
    - If all the consented subjects are eligible, the multisite coordinator emails an accrual closure notice

4.13 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last scheduled procedure shown in the calendar of events, or has been discontinued. The end of study period for the study itself is when the last subject has completed the study.

4.14 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study principal investigator, DSMC, Jazz Pharmaceuticals, and/or sIRB). Written notification, documenting the reason for study suspension or termination will be provided by the suspending or terminating party to study subjects, investigator, funding agency, the Investigational New Drug (IND), Jazz Pharmaceuticals and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) and multisite coordinator will promptly inform study sites, the MCW Institutional Review Board (sIRB), and Jazz Pharmaceuticals and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes. Participating sites will adhere to the sIRB of record's policies.

5 TREATMENT PLAN

Induction therapy – CPX-351

- Drug is to administered according to package insert on days 1, 3 and 5.

The subject is managed as an outpatient, according to the following management plan, including key procedures (outlined in the protocol-mandated study calendar). The following visits are considered minimally necessary, but more frequent visits or outpatient oversight should be conducted as clinically indicated:

- Subject is seen by physician or APP on days 1, 3 and 5 (day of drug administration) and then once weekly until count recovery, or during any period of hospitalization.
- Subject is seen and examined by an oncology-trained nurse on day 6 of treatment, and then, thrice weekly until count recovery.
- Complete metabolic panel (including uric acid, LFTs, phosphorus, creatinine and calcium) is performed daily on days 1, 3, 5, 6 and then thrice weekly until count recovery. Subject's labs are

reviewed by the nurse, discussed with the subject and with the supervising physician or APP (if necessary).
- CBC is performed days 1, 3 and 5 and then thrice weekly until count recovery. Subject's labs are reviewed by the nurse, discussed with the subject, and with the supervising physician or APP (if necessary).
- Subjects and caregivers must have phone access to an MD or midlevel provider for medical triage seven days a week, 24 hours a day.
- Subjects must have access to transfusion support with nursing oversight seven days a week.

5.1 Dose Modification Guidelines

Participating sites should follow package insert for CPX-351 and site standard of care for dose modifications. Any dose modifications may be made according to the attending physician(s) medical decision-making and must be documented in each site's source documents.

5.2 Concomitant and Prohibited Medication

Subjects who are hospitalized will be treated as per institutional guidelines. Except for CNS therapy and the use of hydroxyurea for leukocytosis, CPX-351 should be the sole antileukemia therapy during the duration of subject participation on study. Concurrent/concomitant use of clinically indicated medication is not restricted during protocol therapy.

Sites should consult participating site pharmacist(s) or other reliable drug interaction resource to determine clinical significance and therapy management considerations, as necessary.

5.3 Dietary Restrictions

There are no study-required dietary restrictions.

5.4 Supportive Care Guidelines

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s), within the parameters of the protocol and documented in each site's source documents as concomitant medication.

5.4.1 Antimicrobial Prophylaxis

Prophylactic antimicrobial therapy is required:

- The subject's antimicrobial therapies, and the manner/time of administration, should be explained to the subject. The subject records taking them in the study diary.
- Antibacterial prophylactic therapy may be with a fluoroquinolone or alternative with antipseudomonal coverage according to institutional guidelines.
- Antifungal therapy should be with voriconazole, posaconazole, isavuconazole, micafungin or according to institutional guidelines.
- Antiviral therapy should include prophylactic level acyclovir or valganciclovir. Subject will remain on antimicrobial prophylaxis until (at a minimum) peripheral blood count recovery (or later, as per institutional standards), or antibiotic coverage changes due to infection or other clinical development (i.e., allergy to treatment or development of resistant organism).
- Allopurinol may be administered at the discretion of the physician or medical provider

5.4.2 Myeloid Growth Factors

Prophylactic myeloid growth factors are not to be administered. Treatment with myeloid growth factors during induction should not be used unless they are in the best interest of the subject in the opinion of the treating physician.

5.4.3 Indications for Hospitalization

Subjects will be admitted to the hospital if any of the following criteria are met:

- Subject develops a temperature of > 100.4 F and has an absolute neutrophil count (ANC) below 1,000/µL. Inpatient treatment will be according to standard local institutional practice.
- Subject develops any evidence of significant bleeding or coagulopathy, in the opinion of the treating physician.
- Any medical event, SAE, or other toxicity or complication deemed, in the opinion of the physician or provider, to require inpatient care.

Once the subject is admitted to the hospital, the subject may be discharged back for additional outpatient care if:

- Treating physician believes discharge is medically safe.
- The subject continues to meet logistical criteria.
- There has not been reinduction therapy for persistent disease administered .
- There have been no CNS bleeding events.
- There has been no evidence that the subject is refractory to platelet transfusions.

Upon discharge, the subject again will proceed with the same outpatient laboratory and nurse/physician visit schedule as prior to admission.

5.4.4 Transfusion Support

Transfusion support is required, as follows:

- Prophylactic red cell transfusions for Hemoglobin < 7g/dL
- Prophylactic platelet transfusions for a platelet count below $<11X10^9$.
- Physicians may increase RBC or platelet transfusion threshold, based on local institutional standards, clinical assessment, or follow-up considerations.

5.5 Overdose

Overdose is defined as the following:

- Subject received CPX-351 dose over the institutional rounding standard.

Subjects should be monitored closely for adverse events, if overdose occurs.

Refer to section 6.10 regarding overdose reporting requirements.

5.6 Changes to Site Outpatient Management Capabilities

If a site's outpatient treatment capabilities change after site feasibility approval, the following must occur:

- The site notifies the MCW PI and Multisite Coordinator no later than 5 business days of study staff awareness, clarifying what changed
- The site investigator and MCW PI review for potential issues with protocol requirements
- The MCW PI makes the final determination as to continued site participation

5.7 Subject/Caregiver and Site Communication Plan

Sites must have a detailed communication plan between the subject, caregiver and care team covering the following aspects, at a minimum:

- Specific physician/APP contact information via direct contact, or nurse triage whom the subject may contact regarding symptoms, with 24/7 coverage availability at the site.
    - This should be provided as part of the nurse teacher education program and updated if there are any changes during the course of the trial duration.
- All subjects will carry their site-specific contact information to provide to any/all outside providers regarding their participation in the study, in case they are seen or admitted at an outside facility.
- Contact information of both the subject and caregiver must be checked by site every other week.

Sites should have a detailed communication plan within the participating site itself (i.e., between the research team and other hospital staff at the participating site) covering the following aspects, at a minimum:

- The subject should be flagged as a research subject within the medical record system.
- Specific research staff contact information, that other hospital staff may contact appropriate parties regarding the trial.
- Instructions to hospital staff to notify the site investigator if considering admission.

5.8 Definition of a Protocol-Mandated Appointment

For the purpose of this study, a "protocol-mandated appointment" is defined as visits according to the Schedule of Events calendar.

5.9 Definition of Admission, Provider Recommendation and Inpatient Time

Admission is defined as admission to any treatment center across one midnight.

If a subject is admitted to a treatment center that is not the primary center, the following should occur:

- The enrolling physician (or sub-investigator) should discuss the case with the attending physician.
- At discharge, the enrolling physician (or sub-investigator) should confirm eligibility criteria are obtained, and if not, every effort should be made to correct the situation. If that is not possible, the enrolling physician (or sub-investigator) should recommend admission (at the primary treatment center, if possible).

- The enrolling physician (or sub-investigator) should discuss whether or not the subject should be transferred to the primary center for the remainder of their inpatient care.

Provider recommendation is defined as the following:

- A statement from any physician requesting the subject be admitted for inpatient care. This must be documented accurately in the subject's medical record.

"Inpatient time" is defined as the days spent hospitalized in an inpatient environment between day 1 of induction and count recovery or day 60 (whichever occurs first). This may include more than one admission. We will also collect data on subject hospitalization between day 60 and follow up day 90.

5.9.1 Subject Refusal to be Admitted

A subject's refusal to be admitted is considered "significant noncompliance" and a "significant deviation" (refer to section 6.10). If this occurs, the following must occur:

- A physician must discuss the consequences of the decision and any additional actions the subject may take to ensure additional safety. This must be documented accurately in the subject's medical record.
- The subject must be offered a reeducation opportunity from the nurse teacher.
- The primary caregiver must be notified of the admission refusal.
- Subject will be withdrawn from the study intervention but will be followed as per the study requirements. Follow-up for safety and other endpoints will be performed per physician discretion, with the 30-day and 60-day data follow-up visits if possible.
- Report the refusal expedited according to section 6.10.

5.10 Health-Related Quality of Life Questionnaires

Health-related quality of life questionnaires are collected in the a secure, HIPAA-compliant platform (REDCap) hosted by MCW. Personal health information will not be collected.

During the run-in phase, research staff will seek additional feedback about PROs from the subjects and caregivers in a brief, informal interview (either in-person or by telephone). After completion of the PROs, research staff will review the PRO questions with the participant and take notes to document comprehension of the questions and any other relevant feedback (refer to the Cognitive Interview example). The PROMIS measures are validated so they will not be discussed in detail. The Worries questions are new to this study and will be discussed for participants' interpretation and ease of answering. The team will use the information to amend the PRO assessment prior to the continuation phase.

Both the subject and caregiver complete these assessments of self-reported symptoms and functioning at the following time points (regardless of disease or treatment status, even if the subject is hospitalized):

- Baseline (after consent, but prior to day 1 treatment)
- Seven to 10 days from day 1 treatment
- 30 and 60 days from day 1 treatment

A premade list of all the REDCap questionnaire links for potential site subjects and caregivers is created prior to site activation and provided to participating site staff, who distribute it via email (or it is

completed on a study site electronic device, such as a computer or iPad). For subjects who choose an alternative administration (either one time or exclusively), the following occur:

- Phone
    - Study staff call the subject and caregiver, open the REDCap questionnaire link, ask the questions over the phone, and study staff enter their answers online.
- Paper questionnaires
    - Study staff provides the paper forms.
    - Study staff enters their answers online and uploads the deidentified source document for MCW review.

We have used this alternative approach for previous longitudinal PRO assessments with minimal differences in missing data.[22] Furthermore, PROMIS measures have been evaluated for method of administration effects in a large study of more than 900 US adults, and no meaningful differential item functioning was found between paper, interactive voice response and online modes of administration. [23] There may be differences with interviewer-assisted phone administration, so we will document when phone administration is used so it can be included as a covariate in analysis.

The following process occurs at each collection time point:

- Study staff provides the subject and caregiver their respective links, from the list provided prior to site activation.
- It is the study staffs' responsibility to administer the questionnaires within the allowed window. MCW will periodically monitor that the subject and caregiver questionnaires are completed prior to the end of the allowed window (preferably two business days prior) to attempt to alert the study staff to follow up with the subject and caregiver.
    - Periodic reports of questionnaire completion are provided to study staff.
    - If an assessment is missed or completed outside of the time window, study staff should confirm the reason for the deviation and report it in OnCore.
    - It is better to complete the questionnaires slightly outside of the window than to miss the time point.
- If the seven- to 10day visit was missed, study staff should reeducate the subject on the importance of the QOL trial objectives prior to the day 30 time point.

The selection of the constructs to be measured was based on a review of the literature and we included constructs within physical, mental and social health domains. Where possible, we will use the PROMIS measurement system for these domains for both subjects and caregivers. PROMIS is NIH's initiative to standardize measurement of PROs in clinical research across all chronic conditions. Dr. Flynn was a co-investigator on PROMIS from 2005 to 2015. When PROMIS measures are used, there is the opportunity to compare scores to older conceptually similar domain-specific measures, such as the SF-36. Like the SF-36, PROMIS takes a domain-specific approach to health status. Importantly, PROMIS measures can be administered with computer adaptive testing (CAT) and are validated in multiple languages. CAT is a flexible, computer-driven approach that presents a respondent with items from an item bank. As a subject completes the initial question of a measure's item bank, the CAT algorithm selects only those next items that sharpen the estimate of the subject's score in the domain being measured, **thus decreasing respondent burden as subjects only see questions that are relevant to them. This is especially useful when we expect that there may be large differences in the underlying health of respondents, such as between the subject and caregiver groups.** The domains that we propose to measure are outlined in the **appendix**. Among subjects, we will also measure some treatment-specific toxicities (using the NIH-supported PRO-CTCAE items shown in the appendix) as well as how they prioritize AML-related

worries. [24] We expect the full battery of items to take fewer than 15 minutes to complete, based on our past experience with these measures.

6 Reporting Requirements

6.1 Definition of an Adverse Event

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (International Conference on Harmonisation [ICH], E2A, E6).

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

6.2 Definition of a Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.
- **Life threatening**. Is life threatening (refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization.
- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the subject, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization; any organism, virus or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

6.3 Relationship of an Adverse Event to Study

IMPORTANT NOTE:

For all collected AEs, the site investigator who examines and evaluates the subject must determine the adverse event's causality, based on temporal relationship and clinical judgment, to **BOTH**:

1. Delivery of drug in an outpatient setting, rather than inpatient setting (e.g., caregiver unavailable, travel issue, etc.)

   AND ALSO

2. CPX-351

The degree of certainty about causality will be graded using the categories below:

- **Definitely Related**: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- **Probably Related**: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- **Possibly Related**: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).
- **Unlikely**: A clinical event, including an abnormal laboratory test result, whose temporal relationship to CPX-351 administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- **Unrelated**: The AE is completely independent of CPX-351 administration, and/or evidence exists that the event is definitely related to another etiology.

6.4 Expectedness of an Adverse Event

The **sponsor** is responsible for determining whether an event meets the definition of "unexpected," based on whether the event is listed in the investigator brochure; or if an investigator brochure is not required or available, is not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.

Each site investigator will decide whether an adverse event (AE) is expected or unexpected, but the sponsor is ultimately responsible for determination of expectedness and may therefore override the site investigator's determination of expectedness.

6.5 Routine and Expedited Reporting

IMPORTANT NOTE:

It is expected that all sites will follow best practices to assess AEs and the subsequent attributions for subjects on study. While all AEs will be 'collected' (i.e., recorded in source material such as an electronic medical record), not all AEs are 'reported' centrally (i.e., entered into OnCore data forms or submitted to regulatory agencies). See table below for reporting requirements. Reporting of all events starts after time of consent (such as SAEs prior to enrollment).

Events requiring <u>expedited</u> reporting (i.e., requiring immediate action)	All SAEs.
	All non-hematological Grade 4 AEs not meeting SAE definition.
	Unanticipated problems involving risks to subjects or others (UPIRSO).
	Pregnancy.
	Deviations that are "significant" (e.g., affect safety or trial objectives, subject refusal to be admitted per care team recommendation, etc.), or planned.
	Action letter from Jazz Pharmaceuticals.
	Changes to site outpatient management capabilities
	Subject trial withdrawal.
Events requiring <u>routine</u> reporting (i.e., entered into OnCore in a timely manner)	All hematological Grade 4 AEs and all unexpected Grade 3 AEs (unless in an above category).
Events requiring collection, but not reporting (i.e., not entered into OnCore data forms or submitted to regulatory agencies)	All events not listed above

6.6 Serious Adverse Event Reporting

SAEs are reported in the following manner:

- All SAEs will be reported within 24 hours of study staff awareness using OnCore® (entered in the SAE tab *and* the AE CRF), supporting documents uploaded to Box.com (see below), and email notice sent to the MCW principal investigator and multisite coordinator via the MCW Multisite Team email (who will notify the DSMC Coordinator, as necessary), and to Jazz Pharmaceuticals at AEReporting@jazzpharma.com (see below).
- For all SAEs, the site investigator who examines and evaluates the subject will determine the SAE's causality according to section 6.3.
- Every SAE, regardless of suspected causality (i.e., whether related or unrelated to the study treatment or delivery setting), occurring after the subject has signed the consent through the 30 days after the last dose of CPX-351, **<u>AND only</u>** SAEs occurring more than 30 days after the last dose of CPX-351 that the investigator suspects a causal relationship to CPX-351 **<u>OR</u>** the delivery of drug in an outpatient setting rather than inpatient setting (e.g., caregiver unavailable, travel issue, etc.) must be reported within 24 hours of study staff's awareness using OnCore® (entered in the SAE tab *and* the AE CRF) and via email with the OnCore SAE report and Jazz Pharmaceuticals email confirmation (see below) to the Multisite Coordinator (via. the Multisite Team Email) and MCW principal investigator (who will notify the DSMC Coordinator only if grade 4–5).
- The OnCore® SAE report must be emailed to Jazz Pharmaceutical at AEReporting@jazzpharma.com within 24 hours of study staff's awareness.
- Supporting deidentified source documents (e.g., admission and discharge note) and the email confirmation from Jazz Pharmaceuticals must be uploaded into Box.com within five business days of study staff's awareness.
- If the SAE is serious, unexpected and possibly, probably or definitely related (SUSAR) to

induction drug CPX-351 **OR** is serious, unexpected and possibly, probably or definitely related (SUSAR) to delivery of drug in an outpatient setting rather than inpatient setting (e.g., caregiver unavailable, travel issue, etc.), sites must create a reportable event notice with the sIRB, and complete a MedWatch 3500A and send it in an email to the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email) (who will then email to PVComms@jazzpharma.com and Jazz Pharmaceuticals would report to the FDA if applicable, per postmarketing safety reporting requirements)
    - US FDA MedWatch 3500A may be found here: *http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm*
    - Note that an attribution to the study intervention (i.e., outpatient vs. inpatient setting) may be added to a comment on the MedWatch.
- The DSMC reviews and reports on all applicable AEs and SAEs, which should be submitted by the MCW CTO to the sIRB to assist in their review.
- All SAEs will be followed until satisfactory resolution, or until the site investigator deems the event to be chronic. Any significant update/resolution should be updated in OnCore® follow-up SAE report and an email notice sent to the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email) and Jazz Pharmaceuticals within 24 hours.

6.7 Adverse Events and Grade 4 AEs Not Meeting SAE Definition

It is expected that all sites will follow best practices to assess AEs and the subsequent attributions for subjects on study. While all AEs will be 'collected' (i.e., recorded in source material such as an electronic medical record), not all AEs are 'reported' centrally (i.e., entered into OnCore data forms or submitted to regulatory agencies). See table above for reporting requirements. Reporting of all events starts after time of consent (such as SAEs prior to enrollment).

Any medical condition that is present at the time that the subject is screened (i.e., prior to treatment) will be considered a baseline condition and captured on the baseline OnCore® CRF form, not reported as an AE (though all SAEs that occur during screening are reported in an expedited manner, see below). All new or worsening AEs that occur after starting CPX-351 until 60 days post last dose of CPX-351 (or count recovery, whichever comes first) will be tracked and followed until resolution (i.e., collected but not necessarily reported – see above), subject withdraws consent or is lost to follow-up (including subjects who discontinue early).

Only for those AEs that require reporting: changes (increase or decrease) in the grade of an AE will be documented in the AE CRF to allow an assessment of the duration of the event at each level of severity to be performed. Information to be collected includes event description, time of onset, clinician's assessment of severity, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

Any grade 4 AE that meets the definition of an SAE will be reported according to the manner above for SAEs. Any non-hematological grade 4 AE that does not meet the definition of an SAE will be reported within five calendar days of study staff awareness in the following manner:

- Enter the AE into OnCore® AE CRF
- Email the Multisite Coordinator (via. the Multisite Team Email) and MCW principal investigator (who will notify the DSMC Coordinator) detailing the following information
    - Case/sequence number of subject
    - Date of event
    - CTCAE term

- CTCAE grade
- Relationship to CPX-351 and outpatient setting (outpatient vs. inpatient)
- Expectedness
- Any clinical action taken or planned
- Outcome (if known)

6.8 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (sIRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

UPIRSO Reporting Responsibilities

Note – it is ultimately the MCW principal investigator's (sponsor) responsibility to determine if an event is a UPIRSO or SUSAR from all internal and external safety reports, taking in consideration the information provided by the participating site investigator and commercial manufacturer.

The MCW PI will review each SAE submitted on this study, determine if it qualifies as a UPIRSO, and report it to the sIRB.

The MCW PI will submit a MedWatch form to Jazz Pharmaceuticals (for their postmarketing reporting) only if the MCW study's SAE is suspected, unexpected, AND serious (SUSAR, must meet all three to meeting qualifying criteria).

If the MCW PI identifies a UPIRSO from a qualifying report *on this study* that results in a significant finding/recommendation/action (e.g., change in study conduct, consent, study closure, study hold), it is reported in the following manner:

- The multisite coordinator notifies site principal investigators, site study staff lead contact, the DSMC coordinator, sIRB and Jazz Pharmaceuticals within five calendar days of awareness
- Participating sites report according to local SOPs.
- The multisite coordinator emails the DSMC follow-up letter to site principal investigators and Jazz Pharmaceuticals after completion.

If the MCW principal investigator identifies a UPIRSO from a report *on this study* that does not result in a significant finding/recommendation/action (e.g., change in study conduct, consent, study closure, study hold), it is reported in the following manner:

- The multisite coordinator notifies the DSMC coordinator, sIRB, and Jazz Pharmaceuticals within

five calendar days of awareness
- The multisite coordinator does not email the DSMC follow-up letter to site principal investigators and Jazz Pharmaceuticals, unless requested. These letters are available in Box.

6.9 Reporting Pregnancy

All pregnancies (see below) must be reported in an expended manner from after consent to 90 days post last dose.

Female subjects who become pregnant during CPX-351 administration and within 90 days post last dose of CPX-351 must be taken off CPX-351 immediately and followed, as per the study calendar. Participating sites should report the pregnancy in OnCore as a grade 3 SAE and email the pdf report to the MCW principal investigator, Multisite Coordinator (via. the Multisite Team Email,who will notify the DSMC, as necessary) and Jazz Pharmaceuticals within 24 hours of staff awareness.

If a male subject impregnates his partner during treatment and 90 days post last dose of CPX-351, participating sites should report the pregnancy in OnCore® as a grade 3 SAE and email the pdf report to the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email, who will notify the DSMC, as necessary) within 24 hours of staff awareness.

Whenever possible, a pregnancy (for either a subject or male subject's partner, as described above and according to sIRB policies regarding consent of this partner) should be followed to term, any premature termination reported and the status of the mother and child should be reported after delivery to the Multisite Coordinator (via. the Multisite Team Email) and to Jazz Pharmaceuticals. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

6.10 Protocol Deviations and Overdose

Significant deviations are defined, but not limited to, the following:

- Subject refusal to be admitted, per care team recommendation.
- Enrolling an ineligible subject.
- Deviations that impact subject safety or primary objectives.
- Prohibited medication use.
- Overdose.

Planned deviations are defined as follows:

- Any temporary protocol deviation that is anticipated to occur, but hasn't occurred yet.
- Sites must follow the sIRB's policies regarding acknowledgment prior to deviation initiation.

Significant and/or planned deviations are reported in the following manner:

- Participating sites enter the deviation into OnCore® and email the pdf report to the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email,who will notify the DSMC, as necessary) within five calendar days of staff awareness
- Participating sites report to the sIRB according to their policies and send any acknowledgement letters to the Multisite Coordinator (via. the Multisite Team Email).

Any other deviation that is not significant or planned is to be reported in OnCore® in a timely manner (refer to section 7.11).

The following actions may occur due to persistent or significant deviations:

- Telephone call between the multisite coordinator and site staff to discuss resolution or possible prevention of future deficiencies.
- Schedule additional, or short interval, monitoring visits (remote) and/or training sessions with the multisite coordinator.
- Formal notification to participating site principal investigator of deficit with request for corrective action plan, and/or due date for outstanding items to be completed.
- Warning of potential suspension of participating site accrual until corrective action is completed.
- Suspension of accrual at participating site.
- Participating site accrual closure.

6.11 Jazz Pharmaceuticals Safety Letters and Action Letters

Note – it is ultimately the MCW principal investigator's (sponsor) responsibility to determine a UPIRSO or SUSAR from all internal and external safety reports, taking in consideration the information provided by the participating site investigator and commercial manufacturer.

Jazz Pharmaceuticals will send the MCW study principal investigator, multisite coordinator, and MCW CCCTO primary regulatory contact all external safety letter reports (i.e., from other studies using CPX-351).

If Jazz Pharmaceuticals identifies a UPIRSO from an *external report* that results in a significant finding/recommendation/action (e.g., change in study conduct, consent, study closure, study hold), it is reported in the following manner:

- Jazz Pharmaceuticals sends the report to the MCW study principal investigator, multisite coordinator, and MCW CCCTO primary regulatory contact directly via email in the following manner (i.e., posting reports in an electronic database does not qualify as a means of direct reporting of an unanticipated problem):
    - In each written external safety report that meets qualifying definition, Jazz Pharmaceuticals shall identify all safety reports previously filed with the IND concerning a similar adverse experience and shall analyze the significance of the adverse experience in light of the previous, similar reports.
    - The report should also include the implications for study conduct (i.e., requiring a change in the protocol, such as revising the inclusion/exclusion criteria, new monitoring requirements, informed consent changes, or investigator brochure updates).
    - Follow-up information about a qualifying safety report shall be submitted as soon as relevant information is available.
    - A copy of the updated investigator brochure(s), and/or pertinent study memos regarding direction to be taken by the sites for this safety report.
- The multisite coordinator notifies site principal investigators, site study staff lead contact, the DSMC coordinator, sIRB and Jazz Pharmaceuticals within five calendar days of awareness.
- Participating sites report according to local SOPs.
- The multisite coordinator emails the DSMC follow-up letter to site principal investigators.

If the Jazz Pharmaceuticals identifies a UPIRSO from an *external report* that does not result in a

significant finding/recommendation/action (e.g., change in study conduct, consent, study closure, study hold), it is reported in the following manner:

- No action will be taken, but the MCW principal investigator will have this safety information available to make determinations regarding this study as necessary.

6.12 Changes to Outpatient Management Capabilities

If a site's outpatient treatment capabilities change after site feasibility approval, the following must occur:

- The site notifies the MCW principal investigator and Multisite Coordinator (via. the Multisite Team Email) no later than five business days of study staff awareness, clarifying what changed.
- The site investigator and MCW principal investigator review for potential issues with protocol requirements.
- The MCW principal investigator makes the final determination as to continued site participation.

6.13 Subject Withdrawal

The Multisite Coordinator (via. the Multisite Team Email) and MCW study principal investigator should be notified via email within 24 hours of discontinuation of CPX-351 or study intervention, describing the nature of the discontinuation. OnCore® subject status updates (off treatment date and follow-up start date) and discontinuation eCRF must be completed within 24 hours of discontinuation.

6.14 Staff and Subject Complaint Reporting

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The site principal investigator will be notified of any complaints. Sites report qualifying complaints to the sIRB according to their requirements (refer to sIRB SOPs).

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study, or offer input, the subject can call the research subject advocate. This information is provided to the subject in their consent.

6.15 Reporting UPIRSO to Subjects

The MCW study principal investigator, DSMC, Jazz Pharmaceuticals and/or MCW sIRB may make the determination that an event requires reporting to subjects, either verbally/written documentation or reconsent.

6.16 External or Internal Auditing at Participating Sites

Sites must inform the Multisite Coordinator (via. the Multisite Team Email) of any other external or internal audit/QA review (outside that performed according to this protocol's monitoring and auditing plans) prior to its occurrence, and send the final findings/report, along with any corrective action plan, to the Multisite Coordinator (via. the Multisite Team Email) and MCW principal investigator.

7 OPERATIONAL CONSIDERATIONS, MULTISITE ADMINISTRATION, SOURCE DOCUMENTS, AND DATA MANAGEMENT

7.1 Site Staff Operations

7.1.1 Staff Roles

"Study staff" are key personnel defined by the delegation of authority log and sIRB. They play a significant role in the research, performing an activity regulated by the FDA such as informed consent, assessment of eligibility, assessment of primary endpoints, attribution of adverse events, etc. and are typically the following roles:

- Principal investigator
- Co-investigator
- Nurse teacher
- Clinical research coordinator

7.1.2 Training

All site study staff must be adequately trained to perform the delegated task(s) approved by the participating site principal investigator, as recorded in the delegation of authority log (DOA).

The multisite coordinator may prepare prerecorded training videos and documents, available to sites prior to study activation, and update or provide a supplementary update with each new amendment.

Online training occurs as much as possible. Certificates of completion (or documentation of training) must be available for monitoring/auditing purposes, or upon request.

The MCW templated training log is highly recommended (if a prespecified online log is not utilized). Sites must follow their local SOPs on documentation/process. Site may instead use its own logs if they contain the following information:

- Name of study.
- Item/topic of training (e.g. amendment #2 version date MM/DD/YYYY).
- Printed name and signature/date (if not an online certificate, or electronic confirmation is not obtained) of trainee.
- Method of training (e.g. self-trained PowerPoint review)
- Documentation of who the trainer(s) and trainee(s) were.
- Date when training occurred.

Required items/topics of training may include:

- Site invitation visit (all staff, sections according to their role).
- Amendments (all staff).
- Human subject protection CITI, NIH, etc. (all staff).
- Good Clinical Practice (all staff).
- Principal investigator and co-investigator's CVs and licenses.
- OnCore®/EDC data entry (only staff entering data).

- IATA shipping training (if applicable).
- Other study-specific training (if applicable).

Documentation of completion for required items of training (i.e., training log, CITI completion certification, etc.) and the DOA must be maintained at each site for all study staff members and sent to the multisite coordinator upon request (unless otherwise stated above, typically prior to a monitor visit or audit).

In rare cases, waivers for specific training can be granted on a case-by-case basis, if MCW staff determines that site staff has appropriate experience and/or training. This must be documented and kept on file at each site.

The following situations may require an additional, brief monitoring/training visit with the multisite coordinator:

- When the site consents its first subject.
- Within 24 hours of an SAE.
- After persistent or significant deficiencies.
- In preparation for an audit or data lock.

OnCore® account activation and training occurs in the following manner:

- Training must occur prior to account activation.
- Staff submit the OnCore® Account Request Form and CITI training certificate to the multisite coordinator (if not already available).
- Staff view a prerecorded OnCore® training.
- One-on-one training may be scheduled with the multisite coordinator, as needed.
- OnCore® training materials are provided, along with additional start-up information.
- Completion of training must be documented and maintained by participating sites.

7.1.3 Staff and Protocol Changes

Participating sites should ensure that staff changes occur according to the following method:

- Follow the policies of the sIRB.
- Inform the Multisite Coordinator (via. the Multisite Team Email) immediately when a change in principal investigator or a co-investigator occurs.
    - These changes require the MCW principal investigator review his/her CV, license and CITI training.
    - The MCW principal investigator submits an official approval letter to the participating site prior to performing any study activities.
    - The sIRB of record must approve the change according to their policies.
- Participating sites inform the Multisite Coordinator (via. the Multisite Team Email) when a study staff member joins or no longer participates in the study, and email their required items of training documentation.
- All staff members who no longer participate in the study must have access to all study systems (e.g. OnCore®, Box) removed at the time indicated on the DOA (sites must email the Multisite Coordinator (via. the Multisite Team Email) and OnCore® support team at that time, or prior to it)

The sIRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the sIRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

7.1.4 Delegation of Authority Log

The MCW sIRB templated DOA is required, and states the following:

- Name of study.
- Printed name and signature/date of each staff member.
- A list of delegated task(s) assigned to each staff member, and these cover all possible trial tasks or activities.
- Start and end dates of participation.
- A section for the site principal investigator to sign and date, indicating he/she confirms that the responsibilities and tasks were delegated by him/her and performed by the staff member within the listed effective dates (start and end dates).

7.2 Monitoring Plan

The MCWCC DSMC is responsible for monitoring data quality and subject safety for all MCWCC investigator-initiated clinical trials, according to the approved MCW DSMP.

Unless otherwise specified in the contract/budget, the following monitoring plan will occur under the direction of the multisite coordinator:

- Remote monitoring visits and outstanding data reports approximately every three months (becoming less frequent after the accrual goal is reached, at the discretion of the multisite coordinator)
- Deidentified consents, source documents supporting eligibility, primary and secondary objectives and key data points require upload (refer to section 7.5). The monitor may verify certain data points at his/her discretion.
- Data lock at time of interim analysis (i.e., run-in phase).
- Accrual updates via email approximately every month or three months (depending upon accrual rate or trial activity, at the discretion of the multisite coordinator)
- Study update videoconference meetings may occur approximately every three months (depending upon accrual rate and complexity of trial, at the discretion of the multisite coordinator and MCW principal investigator).

Remote (offsite) monitoring occurs as follows:

- A date and time scheduled between the multisite coordinator and the delegated staff member(s) participating site.
- The visit may occur in a number of different media formats: phone call, web conference (WebEx), video chat, etc.
- The multisite coordinator informs the site about who needs to be in attendance (not everyone needs to be in attendance the entire time).

- Any study related conduct may be discussed (e.g., outstanding data, queries, deviations, issues with accrual, upcoming study updates, regulatory items, etc.).
- If there are significant outstanding items after the remote visit, an additional remote visit may be scheduled within a short time from the initial remote monitoring visit.
- A follow-up letter or email summarizes what was reviewed, any findings or outstanding items, and any required follow-up action or corrective action plan (with a due date).

7.3 Audit Plan

Audit plans are determined by the DSMP according to risk category:

- Approximately 30% of enrolled subjects per site randomly selected for review (a maximum of 10 subjects per site at each review). A previously selected subject may be reselected in a subsequent audit, but all cases since site activation are eligible for selection (despite being enrolled in a period of a prior audit).
- Consent, eligibility and objective-based data are reviewed for all files selected.
- One subject file per site (of the 30% mentioned above) randomly selected for a comprehensive review at each time point.
- 100% of regulatory documents.
- The auditor reserves the right to select another subject(s) if deemed necessary (i.e., in case of a significant or repetitive findings).
- An audit occurs approximately every year until the DSMC determines that future audits may be deferred.

Audits may be performed by either the MCW QA department, a contracted MCW business partner, and/or another entity specified in the consent, contract or budget. Directed audits, outside of those regularly scheduled, may be requested at any time by the multisite coordinator or applicable regulatory agency. Studies are subject to random or for-cause audits from the sIRB.

Participating sites must promptly inform the Multisite Coordinator (via. the Multisite Team Email) of any other external or internal audit/review of this trial prior to its occurrence and send the final findings/report with any corrective action plan to the Multisite Coordinator (via. the Multisite Team Email).

7.4 Audit and Monitoring Report and Corrective Action Plan (CAP)

Audit or monitoring reports occur in the following manner:

- Sent to the participating site principal investigator after the date of the audit or monitoring visit.
- Must be shared with any other required entity as required per local SOPs and policies (e.g., DSMC, sIRB, etc.).
- Includes a brief description of findings.
- Addresses whether a corrective action plan (CAP) is required, and when it is required.
- Indicate if another short-term audit or monitoring visit is necessary, and within what time frame it should occur.

Corrective action plans (CAP) are completed in the following manner:

- The CAP should be a letter that has been reviewed, approved, signed and dated by the participating site principal investigator (may occur electronically).

- The CAP must address *every individual* finding by stating a specific action that will correct the specific finding and prevent it from occurring again (such as improved communication methods, educational opportunities, or quality assurance measures). For example:
    - "The missing source documents for case MCW-VYX-001-P are now uploaded into Box.com. Going forward, this documentation will be uploaded in a timely manner."
    - "The deviation found by the auditor is now entered into OnCore for case MCW-VYX-001-P. We will do X to ensure that this deviation not occur for future subjects."
- The CAP must be emailed to the Multisite Coordinator (via. the Multisite Team Email) and MCW principal investigator.
- The original CAP should be stored in the participating site regulatory binder.
- Subsequent audits or monitoring visits will hold the participating site accountable for the plan.

7.5 Deidentified Source Documents, Remote Access to Records, and Shadow Charts

Regulatory authorities, the sIRB, and/or Jazz Pharmaceuticals may request access to all source documents, data capture records and other study documentation for audit or inspection. Direct access to these documents must be guaranteed by the investigators, who must provide support at all times for these activities.

Sites must adhere to all institutional and sIRB requirements under the Health Insurance Portability and Accountability Act (HIPPA), ensuring all documents and communications are deidentified and secure.

The following deidentified subject/caregiver source documentation must be uploaded into Box.com for each subject in order to confirm eligibility, ensure data quality, and monitor study objectives (this does not apply to the MCW site, as these documents are readily available to the multisite coordinator):

- Consent.
- Reconsent.
- Withdrawal of consent (if applicable).
- Documentation of consent process.
- Supporting documents for all eligibility criteria.
- Reason for ineligibility or treatment/intervention discontinuation (if applicable).
- Supporting documents for important data points (e.g. primary or secondary endpoints).
    - Incidents of noncompliance
        - Physician recommendation to admit inpatient (with reason).
        - Missed scheduled appointments (e.g., provide a log of scheduled appointments and number missed, with reason for missing appointment if available).
    - 30-day and 60-day visits.
    - Documentation of completion of nurse teacher program (for subject and caregiver).
    - Issues of competency with education program, if applicable (see section 4.4.1).
    - Inpatient source (times of admission and discharge, reason for admission, etc.), as necessary.
    - Clarification documents/emails, as requested by the multisite coordinator.
- Source(s) for all expedited reported events.
- SAE supporting source documents (e.g., admission/discharge notes and other applicable procedures) and SAE fax confirmation to Jazz Pharmaceuticals.

If a participating site allows monitors and auditors remote access to its EMR, staff will adhere to their local SOPs.

Shadow charts (e.g., paper or electronic copies of the EMR) are maintained according to local SOPs and site policies.

7.6 Transferring Subjects

If a subject decides to transfer from the enrolling site to another participating site, the following occurs:

- The current enrolling site contacts the multisite coordinator and new participating site.
- Both site principal investigators agree to the transfer and follow institutional SOPs.
- All data and queries must be completed before transfer.
- After any official transfer documents (according to local SOPs and policies) have been finalized:
    - All applicable source documents are transferred.
    - Data capture system access is transferred.
    - The new participating site PI becomes responsible for the subject.

7.7 Data Lock and Verification

A database data lock is facilitated in the following manner:

- The multisite coordinator tracks progress toward the interim analysis time point defined in the protocol.
- The MCW principal investigator sets a data lock date approximately four weeks or more (as necessary) prior to the interim analysis time point or final analysis for publication analysis.
- A remote site monitoring call is scheduled for all participating sites within approximately two weeks prior to the data lock date, at which time all data forms must be complete and up-to-date.
- A reminder may be sent to sites approximately one week prior to the data lock date.
- Data is verified by the participating site principal investigators (see below).
- Data is output from the database on the scheduled data lock date and sent to the statistician for analysis.
- Interim analysis results are reported to the MCW principal investigator, participating sites and Jazz Pharmaceuticals (as necessary).

A participating site principal investigator reviews and verifies all data are complete and accurate in the following manner:

- At the time, data are exported for publication analysis, data are exported from OnCore® by the MCW OnCore® Support Team or multisite coordinator.
- The multisite coordinator sends the data to the participating site principal investigators, who confirm the data are complete and accurate.
- After confirmations, data may then be used by the MCW principal investigator for reporting.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The MCW principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

7.8 Closeout Procedures and Retention of Study Documents

Study closeout confirms that participating sites met study obligations and poststudy obligations are understood.

Closeout activities include the following:

- Verification that study procedures were completed, data collected and data queries addressed.
- Documentation of a plan for retention of study records, and assurance that they are accessible for external audits.
- Reminder to investigators of their ongoing responsibility to maintain study records and to report any relevant study information to the MCW study principal investigator.
- Assurance that participating sites will notify the sIRB of the study completion and store a copy of the notification.
- Closeout letter notifying participating site of study completion.
- Letter to study subjects upon study completion (if required).

7.9 Study Records Retention

Study documents must be retained according to the following requirements (unless otherwise specified in the contract/agreement):

- Participating sites must maintain all study records according to FDA and applicable regulatory requirement(s).
- Records are retained for at least two years after the last marketing application approval or three years after formal discontinuation of the clinical development of the investigational product, or according to applicable regulatory requirement(s), whichever is longest. In either case, sites must inform the MCW study principal investigator and Multisite Coordinator (via. the Multisite Team Email) of any intention to no longer retain study records
- Record retention may be extended per local institution policy.
- If the participating site principal investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.
- The multisite coordinator and MCW study principal investigator must be notified in an email if a custodial change might occur, and approval must be obtained prior to the change.
- Sites must contact the MCW principal investigator and multisite coordinator (who consults with Jazz Pharmaceuticals) prior to destruction of records and obtain prior approval.

7.10 Publication and Data Sharing Policy

Publication and data sharing requirements are detailed in the clinical trial agreement.

The MCW study principal investigator determines authorship in a multifaceted manner, based on substantial intellectual input, effort, and participation.

7.11 Electronic Data Capture and Timely Data Entry

Participating sites enter electronic data into OnCore®, under the supervision and responsibility of the site investigator. Study-specific case report forms (CRFs) will document outcomes. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. Designated study staff will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs. The information collected on CRFs shall be identical to that appearing in original source documents.

The multisite coordinator and MCW support staff are responsible for the monitoring and quality assurance of OnCore® data.

Timely data entry is defined as follows (unless otherwise specified in the contract/budget):

- OnCore® entry must occur within 24 hours of consent, enrollment and withdrawal (for any reason).
- Protocol visit time point data should be entered within 14 days of visit occurrence, unless otherwise requested by the multisite coordinator (e.g., prior to DSMC reviews, audit, etc.).
- Deviations should be entered within 14 days of discovery, if not requiring expedited reporting (refer to section 6.10).
- Refer to section 6 for timely reporting of events requiring expedited reporting.

8 REGULATORY COMPLIANCE, ETHICS AND MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as stated in 21 CFR §312.120(c)(4).

This study will be conducted in compliance with:

- The protocol.
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), and all applicable regulatory requirements. The sIRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

8.1 Prestudy Requirements for MCW

Prior to implementing this protocol at MCW, the protocol, informed consent form, HIPPA authorization and any other information pertaining to subjects must be approved by the MCW sIRB.

8.2 Participating Site Activation Process

8.2.1 Participating Site Selection Criteria

During the site feasibility assessment, the site investigator (with the assistance of site staff members) submits the following documentation for MCW principal investigator review:

1. A signed attestation from the site investigator, stating that the site has confirmed experience with administration of CPX-351 in more than 10 previous subjects.
2. A signed attestation from the site investigator that the site is capable of staffing a site nurse teacher that works in the outpatient environment and is willing to oversee subject education procedures.
3. A signed attestation from the site investigator that the site is capable of performing and reviewing the following outpatient laboratories or procedures seven days a week:
    a. Complete blood count.
    b. Comprehensive metabolic panel.
    c. Transfusions of RBC.
    d. Transfusions of platelets.

4. A signed attestation from the site investigator that the site is capable of receiving and triaging subject phone calls that includes access to a physician with experience in hematology/oncology subjects, an oncology APP, or oncology fellow-in-training, 24 hours a day/seven days a week.
5. A signed attestation from the site investigator that the site is capable of administering CPX-351 inpatient.

8.2.2 Participating Site Feasibility Assessment

The MCW principal investigator recruits and screens potential participating sites.

If a site does not meet the selection criteria, the reason will be documented.

If a site confirms it meets the site selection criteria, the site investigator will submit supporting documentation (refer to section 8.2.1) to the MCW principal investigator for review. If any aspect of the supporting documentation demonstrates a potential issue with the requirements of this protocol, the MCW principal investigator may request additional clarification from the site and confirm or deny participation.

If the MCW principal investigator approves site participation and a nondisclosure agreement is completed by the site, the site investigator reviews the protocol for any potential issue with the requirements compared to site practice and notifies the MCW PI that either no issue is noted, or a potential issue must be resolved. The MCW PI makes the final determination as to continued site participation.

8.2.3 Activation Letter

Study conduct must not occur until an official activation letter has been received at the participating site. After all appropriate institutional and regulatory approvals have been obtained, the MCWCC CTO administrative director, MCW principal investigator and multisite coordinator issue an activation letter to the participating site and study conduct may begin.

Participating sites typically provide the following information to the multisite coordinator prior to activation (as requested by the multisite coordinator):

- Principal investigator statement of adequacy that confirms that the principal investigator "has the appropriate facilities and resources to adequately execute the protocol requirements in the proposed research."
- sIRB approval letter, consent and any other sIRB-approved ancillary document (e.g., QOL questionnaires, subject recruitment materials, etc.)
- Participating site SOPs
    - Consenting.
    - Monitoring/auditing.
    - Other SOPs that the participating site believes may have a foreseeably significant impact on the study (i.e., an SOP that is known to cause issues with other trial sponsors, or an SOP that contradicts anything in the protocol).
- A fully executed contract/agreement and budget.
- Signed 1572 (if applicable, per local SOPs and sIRB).
- Training log.
- SIV training documentation.
- Completed delegation of authority log.
- Principal investigator, sub-investigator, and all study staff CITI Human Subject Protection training certificates.

- Principal investigator and sub-investigator curriculum vitaes (CV) and license(s).
- Financial disclosures.
- Contact information for all relevant staff members.
- Contact information for clinicaltrials.gov website.

8.3 Regulatory Requirements for MCW

All sites must follow all MCW sIRB requirements and policies found here:

https://www.mcw.edu/HRPP/Policies-Procedures.htm

Under the delegation of the MCW principal investigator, the multisite coordinator is responsible for the following:

- Distributing sIRB-approved documents and acknowledgment letters to sites in a timely fashion.
- Obtaining approved regulatory documentation from participating sites and submitting to the sIRB according to sIRB policies.
- Obtaining and reporting information from sites for continuing progress reports (CPRs).
- Facilitating sIRB requests to and from sites.

8.4 Regulatory Responsibilities for Participating Sites

Each participating site has the following regulatory responsibilities:

- Operate under the sIRB and its requirements.
- Report to the MCW sIRB.
- Obtain sIRB approval prior to performing study activity, and maintain approval for the duration of the trial.
- Notify the multisite coordinator of all study updates.
- Inform the multisite coordinator of any other external or internal audit/QA review of a multisite MCW trial prior to its occurrence, and send the final findings/report, along with any corrective action plan, to the multisite coordinator.

8.5 Site Standard Operating Procedures (SOPs)

Participating sites must follow their institutional SOPs regarding all regulatory requirements.

Differences between the protocol and participating site SOPs must be resolved in the following manner:

- It is the participating site's responsibility to find any conflicts/differences between the protocol and SOPs.
- Sites inform the multisite coordinator prior to site activation.
- MCW principal investigator and/or multisite coordinator make the final determination of how to proceed.
- If any SOPs are updated throughout the trial and create a conflict, the participating site must inform the multisite coordinator.

8.6 Continuing Progress Reports

MCW sIRB continuing progress reports are performed in the following manner:

- The multisite coordinator notifies participating sites.
    - An email/letter notice details the specific information requested.
    - The notice is sent prior to submission deadline.
    - A completion deadline will be provided.
- Participating sites provide accurate information (some of which is logged in OnCore®) and emailed to the multisite coordinator.
    - Number of subjects considered (prescreened) for the trial (regardless of consent or eligibility).
    - Number of subjects consented.
    - Number of subjects enrolled.
    - A summary of participating site sIRB approvals (i.e., directly from the electronic submission system is preferred). This can either be a printed website, letter, screenshot, or brief descriptive email. Participating sites must perform a thorough review of this summary. If there is any discrepancy or missing documents/approvals, the multisite coordinator must be informed.
    - A brief descriptive summary of each SAE, deviation, and reportable event (reported from OnCore®).
    - Any internal or external QA or audit reports since the prior progress report.

8.7 CAP, CLIA, and Reference Ranges

Participating sites should ensure their laboratory maintains CAP (if applicable) and CLIA certification. Likewise, if a subject plans to obtain laboratory testing at an outside facility, the participating site should also ensure that the lab is CAP (if applicable) and CLIA certified. The multisite coordinator may request reference ranges as necessary.

8.8 Scientific Review Committee

The MCW Scientific Review Committee (SRC) has the following responsibilities:

- Establishing and maintaining a review committee of sufficient size and breadth of expertise to conduct a critical and fair scientific review of institutional cancer-related research involving human subjects.
- Conducting a thorough scientific review of all non-peer-reviewed, cancer-related clinical protocols using a standard format based on specific, pre-determined review criteria.
- Assisting MCWCC investigators in the development of scientifically and clinically sound research through well-written protocols.
- Considering protocol feasibility with regard to budget, resources and competing trials.
- Establishing clear criteria for determining whether ongoing clinical trials are making sufficient scientific progress, including the attainment of adequate subject accrual rates.
- Monitoring all cancer-related research protocols based on the criteria established by the SRC and terminating protocols that do not meet these expectations.
- Ensures that clinical trials are scientifically sound and that approved trials maintain subject accrual goals and scientific progress.

The levels of reviews are full, expedited or exempt (based on the chair's discretion). Amendments may require SRC review or be exempt from review depending on whether the changes are major or administrative. The SRC may approve, approve with modifications, defer or disapprove a trial.

Furthermore, the SRC identifies low-accruing studies and either warns the disease-oriented team (DOT) chair and MCW principal investigator of low accrual or recommends study closure.

Participating sites will adhere to their local policies regarding scientific review committee approvals.

8.9 Data and Safety Monitoring Committee

The MCW principal investigator only reports DSMC letters to *all other* participating sites if they meet the FDA definition of requiring reporting (i.e., unanticipated problem), are required to be reported to other sites by the DSMC, and/or result in a significant finding/recommendation/action (e.g., change in study conduct, study closure, study hold). However, all DSMC reports can be sent to participating sites upon request.

After DSMC review of a participating site event, the MCW principal investigator reports the DSMC letter to the participating site where the pertinent event occurred.

The most recently approved MCW Data and Safety Monitoring Plan (DSMP) documents must be followed by all participating sites.

The MCW Data Safety Monitoring Committee (DSMC) has the following responsibilities:

- Review the clinical trials for data integrity and safety.
- Review all adverse events requiring reporting as defined per protocol.
- Review all DSM reports.
- Submit a summary of any recommendations related to study conduct.
- Terminate the study if deemed unsafe for subjects.
- Inform the multisite coordinator of finalized reports/letters to be sent to the participating sites.

The DSMC will review reports no less than biannually (unless otherwise specified/approved by the DSMC).

MCW institutional monitoring of multisite trials will be conducted according to the approved Data and Safety Monitoring Plan (DSMP), under the responsibility of the associate director for clinical research (ADCR).

8.10 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and Jazz Pharmaceuticals and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data and all other information generated will be held in strict confidence.

The study monitor, other authorized representatives of the Jazz Pharmaceuticals, representatives of the Institutional Review Board (sIRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in OnCore®. This will not include the subject's contact or identifying information from participating sites outside MCW. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by MCW research staff will be secured and password protected. At the end of the study, all study databases (e.g., OnCore® data) will be archived at the Medical College of Wisconsin.

8.11 Risk Management

8.11.1 Risk Assessment, Control and Review

Risk management occurs through a collaborative effort between the MCW principal investigator, MCWCC DSMC, sIRB and multisite coordinator. Risk assessment, control, and review plans are based on risk categories (low, intermediate, or high), which determine the audit/monitoring plan (refer to section 7.2).

Risk assessment occurs throughout the trial through identification (based on previous data and events reported during the trial) and analysis of risks (e.g., statistical methods, refer to section 9). Risk control methods are defined in this protocol, and enacted by site investigators, through the following control plan:

- Reduction of risks
    - Dose reduction
    - AE management
    - Concomitant and prohibited medications
- Acceptance of risks
    - Risk-benefit ratio
    - Efficacy of control methods
    - Clinical significance

Risk reviews occur through the following methods:

- Review of risks
    - Stopping rules
    - Interim analysis
    - Risk-benefit ratio
    - DSMC review
    - sIRB review
- Feedback into assessment and control
    - Changes to risk assessment and control plan
- Facilitating actions
    - Consent risk changes
    - Protocol procedure changes (e.g. adding a test to ensure subject safety)
    - Changes in monitoring and auditing (e.g. increasing frequency of visits)
    - Accrual suspension or closure

8.11.2 Safety Run-In Phase and Continuation Phase

To ensure initial feasibility and subject safety, this trial will consist of a safety run-in phase with only six subjects, then subsequently a DSMC safety analysis of those six subjects and a continuation phase enrolling the rest of the accrual goal.

After the 60-day mortality follow-up occurs for the sixth subject, the DSMC will be notified by the multisite coordinator and data provided for a safety analysis. The DSMC and/or MCW principal investigator may recommend changes to the protocol's risk assessment and control plans (see above).

If the run-in phase stopping rules are met (refer to section 9.4), or the DSMC and/or MCW principal investigator recommend closing accrual for any other concern, the trial will close to accrual. Otherwise, the DSMC may approve further accrual on the continuation phase and audit/monitor the trial according to the continuation phase risk assessment, control and review plans.

8.11.3 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the sIRB mechanism and the informed consent process. The sIRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The sIRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

8.12 Changes in the Protocol, Consent or other Trial Document

A participating site may request changes to trial documents in the following manner:

- Major site-specific changes to the consent and ancillary documents are highly discouraged, though some changes are necessary (e.g., accrual goal updates, local context changes, etc.)
- Any change must be clearly indicated, then submitted to the multisite coordinator for approval by the MCW principal investigator, Jazz Pharmaceuticals (if required) and sIRB, prior to implementation
- MCW principal investigator and sIRB approval must occur prior to implementation of any change, unless *all* of the following apply:
    - Approval cannot be obtained in a reasonable time frame for subject safety and must be implemented immediately for subject safety.
    - The MCW principal investigator, multisite coordinator and applicable agencies (Jazz Pharmaceuticals, sIRB) are informed as soon as possible, if they cannot be informed before implementation.
    - The investigator must then notify the sIRB in writing within five calendar days after implementation.

The sIRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the Jazz Pharmaceuticals and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the Jazz Pharmaceuticals.

9 STATISTICAL CONSIDERATIONS

9.1 Aims

Primary Aim

To estimate the feasibility of an outpatient care model for induction and management of subjects with AML who receive induction therapy with VYXEOS.

Secondary Aims

1. To estimate the overall inpatient time for subjects who receive VYXEOS induction as an outpatient. The estimation will include all time between day 1 and count recovery or day 60, whichever occurs first.
2. To estimate the incidence of admission to an intensive care unit in subjects treated in an outpatient environment.
3. To estimate the incidence of 30-day all-cause mortality in subjects treated in an outpatient model.
4. To estimate the incidence of 60-day all-cause mortality in subjects treated in an outpatient model.
5. To describe the resource utilization for subject induced as outpatients.
6. To assess the quality of life, anxiety levels and health care priorities for subjects receiving induction chemotherapy in an outpatient environment at the time of induction, 7–10 days following induction, and 30 and 60 days after induction.
7. To assess the quality of life anxiety levels and health care priorities for the primary caregiver of subjects receiving induction chemotherapy in an outpatient environment at the time of induction, 7–10 days following induction, and 30 and 60 days after induction.

Primary hypotheses:

- The probability of successful outpatient treatment delivery (SOTD), as defined in Section 2.3, exceeds 70%.

Secondary hypotheses:

- The incidence of 30-day mortality after the start of induction does not exceed 6%.
- The incidence of 60-day mortality after the start of induction does not exceed 14%.

9.2 Sample Size Determination and Power Estimate

With 120 subjects, the study will have 80% power at a one-sided 5% significance level demonstrate probability of successful outpatient treatment exceeding 70% if the underlying probability is 80%.

9.3 Subject Replacement

Subjects who sign the informed consent form but are not enrolled may be replaced (i.e., doesn't count toward the 120 enrollment goal). However, as the primary outcome of the study is feasibility, and noncompliance, withdrawal of consent, or inability to receive study intervention are indicators of lack of feasibility, once a subject is enrolled, they will not be replaced and such withdrawals will be counted as events for the SOTD outcome.

9.4 Stopping Rules

The study will be monitored for safety via stopping rules for 30-day and 60-day all-cause mortality. The monitoring rules were derived assuming an acceptable rate of 6% and 14% for 30- and 60-day mortality, a one-sided significance level of 10% with evaluation after every 20th subject. An additional evaluation will

be performed at the end of the safety run-in phase of six subjects. The study will be stopped for DSMC review if the number of deaths exceeds the cutoff values shown in Table 1.

Table 1: Safety monitoring boundaries for mortality

Number of evaluable subjects	Maximum allowable deaths within 30 days	Maximum allowable deaths within 60 days
6	1	2
20	3	6
40	6	10
60	7	13
80	9	17
100	10	20
120	12	24

Table shows the probability of crossing these boundaries for several values of the underlying probability of mortality.

Table 2: Probability of crossing the mortality monitoring boundaries. The design settings are bolded.

Underlying event probability	30-day mortality		60-day mortality	
	Probability of crossing boundary	Expected sample size	Probability of crossing boundary	Expected sample size
6%	**11%**	**110.6**	<1%	119.6
10%	56%	82.7	2%	117.9
14%	92%	51.0	**10%**	**111.9**
18%	>99%	32.0	39%	95.7
22%	>99%	22.4	76%	71.1
24%	>99%	19.4	88%	59.3

9.5 Interim Analysis

No interim analyses for efficacy are planned. Interim analyses for safety, including a check after the first six subjects are described in Section 9.4.

9.6 Analysis Method

The demographics of the subject population will be reported using appropriate descriptive statistics, such as frequencies and percentages with standard errors for categorical variables, mean with standard error or median with quartiles for continuous variables.

Primary outcome

The probability of SOTD will be estimated as the observed proportion and reported with a 90% confidence interval. The primary hypothesis of the probability of SOTD exceeding 70% will be tested using a one-sided z-test at a 5% significance level. Statistical significance will be observed if at least 93 of the 120 subjects achieve the outcome, for an observed probability of 77.5% or higher. For subjects who do not achieve SOTD, the reasons of failure will be tabulated.

Secondary outcomes

Overall inpatient time will be quantified as days being admitted and set to zero for subjects without an inpatient admission. Descriptive statistics will be presented both overall and among admitted subjects.

The risk for admission to an intensive care unit will be estimated as the observed proportion and presented with 90% confidence interval.

Overall survival will be visualized using the Kaplan-Meier estimate. Values corresponding to 30-day and 60-day mortality will be presented separately.

PROs - Data Management

All data will be stored securely in REDCap. Personal health information will be kept separately, and only key participating site staff will have access to the identifiers linking clinical and personal data.

PROs - Analyses

We will analyze the different domains of subjects' symptoms and functioning separately (that is, depression separate from fatigue separate from physical function, etc.), since combining them into a summary score can dilute the effects of the individual (and not necessarily related) components and thus mask true change. The measures will be reported with mean and standard errors for each time point. Changes in the PRO measures over time will be analyzed by repeated measures analysis with a random subject-specific intercept. The estimated mean changes will be reported with 95% confidence intervals.

PROs - Prevention and Management of Missing Data

We expect two potential sources of missingness of PROs: subject death during the study and subject nonresponse to an entire questionnaires or specific items. Different approaches will be used for these two sources of missingness.

We will make every effort to limit subject nonresponse to an entire questionnaire. The MCW multisite coordinator will monitor the subject and caregiver data collection through REDCap, and reminders will be sent for uncompleted surveys.

We will handle item-level missing values in each domain using the following approach. If at least 50% of the items per domain were answered, then we will adjust the score to ([Raw sum x number of items in the domain] / number of items answered). If fewer than 50% of the items in a domain were answered, we will treat the domain as missing. The random effects repeated measures modeling approach is well suited for the incorporation of missing-at-random outcomes without imputation. We will describe any differences in patient characteristics between responders and nonresponders and adjust the analyses for any predictive covariates.

Missing PROs due to the subject's death will be accounted for using two complementary approaches: unconditional and conditional analysis. In the unconditional analysis, the lowest possible value for the measure will be imputed for subjects who died, treating death as the extreme of the quality of life scale. In the conditional analysis, the PRO responses will be evaluated conditional on the subject being alive. This analysis will be performed using a semicontinuous repeated measures model that includes a binary indicator of being alive at each time point and estimates the effect of time on PRO values only among patients who are alive.

10 REFERENCES

1. Estey E. Reducing mortality associated with immediate treatment complications of adult leukemias. Semin Hematol. 2001; 38:32–37.

2. Appelbaum FR et al. Age and acute myeloid leukemia. Blood. 2006; 107:3481–3485.

3. Vaughn JE et al. Resource Utilization and Safety of Outpatient Management Following Intensive Induction or Salvage Chemotherapy for Acute Myeloid Leukemia or Myelodysplastic Syndrome: A Nonrandomized Clinical Comparative Analysis. JAMA Oncol. 2015; 1(8): 1120–1127.

4. Halim TY et al. Positive impact of selective outpatient management of high-risk acute myelogenous leukemia on the incidence of septicemia. Ann Oncol. 2007 Jul;18(7):1246-52.

5. Getz KD et al. A comparison of resource utilization following chemotherapy for acute myeloid leukemia in children discharged versus children that remain hospitalized during neutropenia. Cancer Med. 2015;4(9):1356-64.

6. Møller T et al. Safe and feasible outpatient treatment following induction and consolidation chemotherapy for patients with acute leukaemia. Eur J Haematol. 2010 Apr;84(4):316-22.

7. Khouri J, Majhail NS. Advances in delivery of ambulatory autologous stem cell transplantation for multiple myeloma. Curr Opin Support Palliat Care. 2017 Dec;11(4):361-5.

8. Martino M et al. A Comparative Assessment of Quality of Life in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation Through an Outpatient and Inpatient Model. Biol Blood Marrow Transplant. 2018;24(3):608-613.

9. Othus M et al. Declining Rates of Treatment-Related Mortality in Patients with Newly-diagnosed AML Given “Intense” Induction Regimens: A Report from SWOG and MD Anderson. Leukemia. 2014 Feb; 28(2): 289–292.

10. Percival ME, Tao L, Medeiros BC, Clarke CA. Improvements in the early death rate among 9380 patients with acute myeloid leukemia after initial therapy: a SEER database analysis. Cancer. 2015; 121:2004–2012.

11. Vaughn JE, Buckley SA, Walter RB. Outpatient care of patients with acute myeloid leukemia: Benefits, barriers, and future considerations..Leuk Res. 2016; 45: 53–58.

12. Redaelli A, Botteman MF, Stephens JM, Brandt S, Pashos CL. Economic burden of acute myeloid leukemia: a literature review. Cancer Treat Rev. 2004; 30:237–247.

13. Nerich V et al. Induction-related cost of patients with acute myeloid leukemia in France. Int J Clin Pharm. 2011; 33:191–199.

14. Leunis A, Blommestein HM, Huijgens PC, Blijlevens NM, Jongen-Lavrencic M, Uyl-de Groot CA. The costs of initial treatment for patients with acute myeloid leukemia in the Netherlands. Leuk Res. 2013; 37:245–250.

15. Irish WD, Ryan M, Gache L, Gunnarsson C, Bell T, Shapiro M. Acute myeloid leukemia (AML): a retrospective claims analysis of resource utilization and expenditures [abstract] Blood. 2015; 126:5633.

16. Walter RB, Lee SJ, Gardner KM, Chai X, Shannon-Dorcy K, Appelbaum FR, Estey EH.. Outpatient management following intensive induction chemotherapy for myelodysplastic syndromes and acute myeloid leukemia: a pilot study. Haematologica. 2011; 96(6):914-917.

17. Walter RB, Taylor LR, Gardner KM, Dorcy KS, Vaughn JE, Estey EH. Outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia. Clin Adv Hematol Oncol. 2013;11(9):571-577.

18. Vaughn JE et al. Resource Utilization and Safety of Outpatient Management Following Intensive Induction or Salvage Chemotherapy for Acute Myeloid Leukemia or Myelodysplastic Syndrome: A Nonrandomized Clinical Comparative Analysis. JAMA Oncol. 2015; 1(8):1120-7.

19. Lancet JE et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. Blood. 2014; 123(21): 3239–3246

20. Lancet JE et al. CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients with Newly Diagnosed Secondary Acute Myeloid Leukemia. J Clin Oncol. 2018 Sep 10;36(26):2684-2692

21. Kolitz JE et al. Efficacy by consolidation administration site: Subgroup analysis of a phase III study of CPX-351 versus 7+3 in older adults with newly diagnosed, high-risk acute myeloid leukemia (AML). Journal of Clinical Oncology 2017 35:15_suppl, 7036-7036

22. Williams MS, Snyder DC, Sloane R, Levens J, Flynn KE, Dombeck CB, et al. A comparison of cancer survivors from the PROMIS study selecting telephone versus online questionnaires. Psychooncology. 2013;22(11):2632-5.

23. Bjorner JB, Rose M, Gandek B, Stone AA, Junghaenel DU, Ware JE, Jr. Method of administration of PROMIS scales did not significantly impact score level, reliability, or validity. Journal of clinical epidemiology. 2014;67(1):108-13.

24. Bridges JF, Oakes AH, Reinhart CA, Voyard E, O'Donoghue B. Developing and piloting an instrument to prioritize the worries of patients with acute myeloid leukemia. Subject Prefer Adherence. 2018 Apr 27; 12:647-655.

APPENDIX 1: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2: Lost to Follow-Up Letter

Please use the form on the next page.

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial in which you participate.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at _____

Sincerely,

_____

APPENDIX 3: Prescreening Log

Refer to sIRB of record policies regarding prescreening and screening.
Send to the Multisite Coordinator upon request.

Study: _____ Site: _____ **Participating site PI signature/date (at study closure): _____**

Subject # (deidentified)	**Date of contact**	**Discussed trial with subject or given consent?** Yes/No	**Consented?** Yes/No	**Reason subject refused consent?** i.e., risks considered to outweigh potential benefits (specify), decision to pursue another treatment options (specify), cost, lost to follow-up or unknown, etc.	**Which specific eligibility criteria was not met?** e.g., inclusion criteria 3

APPENDIX 4: NURSE TEACHER EDUCATION PROGRAM VALIDATION GUIDE

After completing the standardized education with the subject and caregiver, review the following key points to assure information has been understood and the outpatient management plan will be followed in a safe manner.

1. Validate that subject/caregiver has the following items at home or can verbalize plans to obtain prior to treatment start date.
    a. Thermometer
    b. Reliable telephone(s)
        i. Charging accessories for mobile devices
    c. Reliable transportation
2. Ask the subject to teach-back about each of the following topics at a minimum. Assure the key points are addressed. Reinforce education if there are missed items.
    a. Temperature monitoring
        i. Take temperature two times per day
        ii. Call if temperature is 100.4°F or greater
    b. Infection prevention
        i. Hand hygiene
    c. Pregnancy prevention
        i. Effective birth control method for subject's gender
    d. How to contact the doctor and/or clinic
    e. Caregiver accountabilities
        i. Availability
        ii. Transportation
        iii. Assistance
    f. Subject accountabilities
        i. Timely communication of new or concerning symptoms
        ii. Attend appointments
        iii. Take medications
        iv. Answer clinic phone calls
        v. Follow doctor recommendations

Provide subject and caregiver with handout slides reinforcing key points.

Subject and Caregiver ID _____

"I verify that the subject and caregiver have completed and adequately understand the study-dictated nurse teacher educational program. I verify the subject and caregiver have capacity to comply with outpatient management program".

_____ _____

Nurse Teacher Name (printed) and Signature/Date

APPENDIX 5: STUDY DIARY

Subject Instructions:

Please bring this study diary to all scheduled hospital visits.

Make sure to call or page your care team for any other new or concerning symptoms. You may also record them on the study diary, but do not hesitate to call for anything of concern. Especially for symptoms like pain, nausea, vomiting, rash, oral or dental problems, intestinal problems like diarrhea or constipation, or any other concern for you or your caregiver.

If your temperature is 100.4 °F or more:

- Call or page your physician right away. Use the contact information provided during your educational session.
- Follow that physician's instructions regarding next steps.
- Have your caregiver bring you to the hospital right away. If that caregiver is not available, please either call 911 to have an ambulance attend to you OR ask your physician if you are safe to drive yourself.

Emergency information for other hospitals:

This subject is on a clinical trial examining the safety of outpatient CPX-351 AML treatment. Please contact the site investigator if the subject presents to your hospital.

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Subject signature and date:_____ **PAGE 2 of 8**

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Subject signature and date:_____ **PAGE 5 of 8**

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Subject signature and date:_____ **PAGE 6 of 8**

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Subject signature and date:_____**PAGE 7 of 8**

Study Diary

Subject # (completed by hospital): _____

Date	Time	Temperature °F	Medication Taken?			Any new or worsening side effects or symptoms? Describe
			Antifungal	Antibacterial	Antiviral	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	
			Yes No	Yes No	Yes No	

Subject signature and date:_____**PAGE 8 of 8**

APPENDIX 6: PATIENT-REPORTED OUTCOME MEASURES

PROMIS Item Bank v.1.0 - Fatigue -Short Form 7a

FATIGUE - SHORT FORM 7A

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

2 May 2016

EMOTIONAL DISTRESS-ANXIETY – SHORT FORM 4A

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
EDANX01	I felt fearful.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2 June 2016

EMOTIONAL DISTRESS-DEPRESSION – SHORT FORM 4A

Please respond to each question or statement by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

26 June 2016

PHYSICAL FUNCTION – SHORT FORM 8b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC12	Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

23 June 2016

SLEEP DISTURBANCE – SHORT FORM 4A

Please respond to each question or statement by marking one box per row.

In the past 7 days…

		Very poor	Poor	Fair	Good	Very good
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

ABILITY TO PARTICIPATE IN SOCIAL ROLES AND ACTIVITIES - SHORT FORM 4A

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
SRPPER11_ CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_ CaPS	I have trouble doing all of the family activities that I want to do.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_ CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_ CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

23 June 2016

INSTRUMENTAL SUPPORT – SHORT FORM 4A

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
CCC31052x	Do you have someone to help you if you are confined to bed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
CCC31055x	Do you have someone to take you to the doctor if you need it?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
CCC31065x	Do you have someone to help with your daily chores if you are sick?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SS6	Do you have someone to run errands if you need it?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

EMOTIONAL SUPPORT – SHORT FORM 4A

Please respond to each item by marking one box per row.

		Never	Rarely	Sometimes	Usually	Always
FSE31053x2	I have someone who will listen to me when I need to talk.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FSE31059x2	I have someone to confide in or talk to about myself or my problems	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SS12x	I have someone who makes me feel appreciated	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
SSQ3x2	I have someone to talk with when I have a bad day	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

23 June 2016

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 5 September 2018

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly

5.	In the last 7 days, did you have any RASH?	
	○ Yes	○ No

6.	In the last 7 days, did you have any HAIR LOSS?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 5 September 2018

7.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, what was the SEVERITY of your BLURRY VISION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did BLURRY VISION INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0
English
Form created on 5 September 2018

Outpatient treatment worries and burden of subjects with AML

We are interested in understanding how people feel about getting intensive induction chemotherapy for leukemia as an outpatient, meaning that they come in regularly to the clinic to receive therapy instead of staying in the hospital.

1. How worried are you about getting intensive induction chemotherapy as an outpatient?
2. How worried are you about having medical complications at home?
3. If you have complications at home, how worried are you about being able to quickly reach your doctors by phone?
4. If you have complications at home, how worried are you about being able to quickly reach your nurses by phone?
5. How worried are you about being a burden to your loved one or caregiver?

1 = not at all worried
2 = a little worried
3 = somewhat worried
4 = quite worried
5 = very worried

6. How confident are you that your loved one or caregiver is able to take care of you at home?
7. How confident are you that your loved one or caregiver can manage your daily medical needs?
8. How confident are you that your loved one or caregiver can manage any complications?

1 = not at all confident
2 = a little confident
3 = somewhat confident
4 = quite confident
5 = very confident

At 30 days, only:

9. Please describe any additional worries that you have experienced during the last 30 days. [Textbox]

Outpatient treatment worries of caregivers of subjects with AML

1. How worried are you about being the primary caregiver for your loved at home?
2. How worried are you about your loved one having medical complications at home?
3. How worried are you about being able to quickly reach your loved one's doctors by phone?
4. How worried are you about being able to quickly reach your loved one's nurses by phone?
5. How worried are you about feeling that your loved one is a burden?

1 = not at all worried
2 = a little worried
3 = somewhat worried
4 = quite worried
5 = very worried

6. How confident are you that you are able to take care of your loved one at home?

7. How confident are you that you are able to manage daily medical needs for your loved one at home?

8. How confident are you that you can manage any complications of your loved one's therapy?

9. How confident are you that you can provide self-care while taking care of your loved one?

1 = not at all confident
2 = a little confident
3 = somewhat confident
4 = quite confident
5 = very confident

At 30 days, only:
10. Please describe any additional worries that you have experienced during the last 30 days. [Textbox]

Demographics

Please tell us about yourself.

What is your gender?

- ◯ Male
- ◯ Female
- ◯ Something else
- ◯ I prefer not to answer

Please explain, "Something else".

_____

What is your age?

_____

What is your marital status?

- ◯ Married or living like married
- ◯ Widowed
- ◯ Divorced
- ◯ Separated
- ◯ Single, never married
- ◯ Other
- ◯ I prefer not to answer

What is your ethnicity?

- ◯ Hispanic or Latino
- ◯ Not Hispanic or Latino
- ◯ I prefer not to answer

What is your race?

Please check all that apply.

- ☐ White or caucasian
- ☐ Black or African American
- ☐ Asian or Asian American
- ☐ American Indian or Alaska Native
- ☐ Native Hawaiian or other Pacific Islander
- ☐ Other
- ☐ I prefer not to answer

What is the highest degree or level of school that you have completed?

- ◯ No schooling completed
- ◯ Nursery school to 5th grade
- ◯ 6th to 8th grade
- ◯ 9th to 12th grade (no diploma)
- ◯ High school diploma or equivalent (GED)
- ◯ Some college, no degree
- ◯ Associate's degree
- ◯ Bachelor's degree
- ◯ Master's degree
- ◯ Doctoral or professional degree
- ◯ I prefer not to answer

What statement best describes your current employment status?

- ◯ Working - as a paid employee
- ◯ Working - self-employed
- ◯ Not working - on temporary layoff from a job
- ◯ Not working - looking for work
- ◯ Not working - retired
- ◯ Not working - on disability
- ◯ Not working - other
- ◯ I prefer not to answer

What is your total HOUSEHOLD income in the past 12 months?

- ◯ Less than $20,000
- ◯ $20,000 to $39,999
- ◯ $40,000 to $59,999
- ◯ $60,000 to $79,999
- ◯ $80,000 to $99,999
- ◯ $100,000 to $199,999
- ◯ $200,000 or more
- ◯ I prefer not to answer