SUMMARY OF CHANGES

Longitudinal Quality of Life Study among Participants with AIDS-Associated Kaposi Sarcoma at Bugando Medical Centre, in Mwanza, Tanzania

Version 2.0

NCI Protocol #: AMC-S007
Local Protocol #: AMC-S007

NCI Version Date: 20MAR2018
Protocol Date: 20MAR2018

#	Section	Comments
1.	Global	*Changed from:* Version 1.0, **21NOV2017** NCI Version **21NOV2017** *Changed to:* Version 2.0, **20MAR2018** NCI Version **20MAR2018**
2.	Global	*Changed from:* Common Terminology Criteria for Adverse Events version **4**.0 (CTCAE v**4**.0) *Changed to:* Common Terminology Criteria for Adverse Events version **5**.0 (CTCAE v**5**.0)
3.	6.3.3	*Changed from:* Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)" under the system organ class (SOC) of the same name**. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted. *Changed to:* Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions – Disease Progression"**. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
4.	6.3.4	*Changed from:* Pregnancy reporting and outcomes will be documented by completion of the appropriate CRFs, including the Adverse Event form. *Changed to:* Pregnancy reporting and outcomes will be documented by completion of the appropriate CRFs, including the Adverse Event form, **using the appropriate term in the system organ class (SOC) for Pregnancy, puerperium and perinatal conditions**.

#	Section	Comments
5.	8.1.5	*Changed from:* Complete blood cell counts with differentials and platelets, and serum liver/renal function analysis. This should include the following: **albumin, alkaline phosphatase,** total bilirubin, **bicarbonate, BUN, calcium, chloride,** creatinine, **glucose, LDH, phosphorus, potassium, total protein,** SGOT [AST], SGPT [ALT], **sodium**. *Changed to:* Complete blood cell counts with differentials and platelets, and serum liver/renal function analysis. This should include the following: total **and direct** bilirubin, creatinine, SGOT [AST], SGPT [ALT].
6.	Appendix I	*Changed from:* Instructions: **In the event that** the participant's condition is deteriorating, laboratory evaluations should be repeated within 24 hours before initiation of the next cycle of therapy. Footnote a: **Albumin, alkaline phosphatase, total** bilirubin, **bicarbonate, BUN, calcium, chloride,** creatinine, **glucose, LDH, phosphorus, potassium, total protein,** SGOT [AST], SGPT [ALT], **sodium**. *Changed to:* Instructions: **If** the participant's condition is deteriorating, laboratory evaluations should be repeated within 24 hours before initiation of the next cycle of therapy. Footnote a: **Total and direct** bilirubin, creatinine, SGOT [AST], SGPT [ALT].

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL #S007:

Longitudinal Quality of Life Study Among Participants with AIDS-Associated Kaposi Sarcoma at Bugando Medical Centre, in Mwanza, Tanzania

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	TBD
Regulatory Status:	Subject to Review by the BMC/CUHAS Research Ethics Committee and the Tanzanian National Institute for Medical Research (NIMR)
Commercially Available Agents:	Bleomycin (NSC 125066) Vincristine sulfate (NSC 67574)
Protocol Chair:	Kristin Schroeder, MD, MPH
Protocol Co-Chair:	Nestory Masalu, MD, MMed

Version 2.0
20 March 2018
NCI Version 20 March 2018

AMC PROTOCOL SIGNATURE PAGE

I, Nestory Masalu, Principal Investigator at site Bugando Medical Centre agree to conduct and follow this protocol: **AMC Protocol #S007 – Longitudinal Quality of Life Study Among Participants with AIDS-Associated Kaposi Sarcoma at Bugando Medical Centre, in Mwanza, Tanzania (Version 2.0, 20MAR2018),** as written according to AMC, NCI, and National Institute for Medical Research (NIMR) guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (dd/mmm/yyyy)

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

PROTOCOL ROSTER

AMC Protocol #S007
Longitudinal Quality of Life Study Among Participants with AIDS-Associated Kaposi Sarcoma at Bugando Medical Centre, in Mwanza, Tanzania

Protocol Chair:
Kristin Schroeder MD, MPH
AIDS Malignancy Consortium
P.O. Box 1370
Mwanza, Tanzania
Tel: 255-686-3-86349
Email: kristin.schroeder@dm.duke.edu

Protocol Statistician:
Jeannette Y. Lee, PhD
AMC Statistical Center
University of Arkansas for Medical Sciences
4301 W. Markham, #781
Little Rock, Arkansas 72205-7199
Tel: (501) 526-6712
Fax: (501) 526-6729
Email: JYLee@uams.edu

Protocol Co-Chair:
Nestory Masalu MD, MMed
Bugando Medical Centre
P.O. Box 1370
Mwanza, Tanzania
Tel: 255-783-0-00004
Email: nmasaslu4@gmail.com

Data Management/Operations:
AMC Operations and Data Management Center
The Emmes Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850
Tel: (301) 251-1161
Fax: (240) 238-2842
Email: amipm@emmes.com

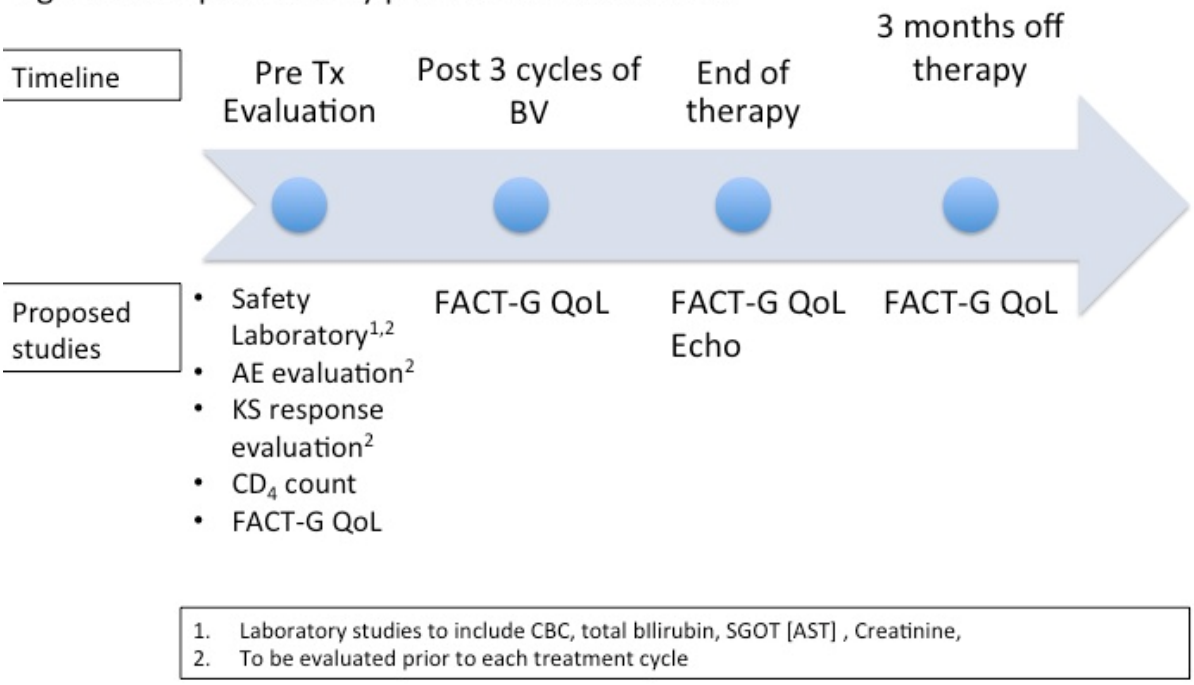
AMC Kaposi Sarcoma Working Group Chair:
Lee Ratner, MD, PhD
Washington University School of Medicine
Division of Oncology
660 S. Euclid Avenue
Campus Box 8069
St. Louis, MO 63110
Tel: 314-362-8836
Fax: 314-747-2120
Email: lratner@dom.wustl.edu

PROTOCOL SYNOPSIS

TITLE:	Longitudinal Quality of Life Study Among Participants with AIDS-Associated Kaposi Sarcoma at Bugando Medical Centre, in Mwanza, Tanzania
PHASE OF STUDY:	Pilot
PARTICIPATING INSTITUTIONS:	This protocol will be open at the Bugando Medical Centre in Mwanza, Tanzania
ACCRUAL TARGET:	Minimum: 12, Maximum: 20
POPULATION:	Participants with KS who are HIV-positive initiating chemotherapy with bleomycin and vincristine sulfate (BV). See Section 3.0 for eligibility criteria.
REGIMEN:	Participants will receive standard therapy for KS: bleomycin (15 units/m^2) and vincristine (2mg fixed dose) infused intravenously every 21 days for a maximum of six cycles. A Quality of Life (QOL) survey, the Functional Assessment of Cancer Therapy-General (FACT-G), will be administered at baseline, after 3 and 6 cycles of treatment (cycle 4 and treatment discontinuation), and at 3 months after treatment discontinuation.
DURATION:	7 months
PRIMARY OBJECTIVE:	To evaluate the longitudinal quality of life of participants with HIV-associated KS during treatment with vincristine and bleomycin at a single institution in East Africa.
SECONDARY OBJECTIVE:	To explore baseline and time-dependent correlates of improvements in quality of life.
EXPLORATORY OBJECTIVE:	To assess quality control (completeness and accuracy) in data capture of adverse events, clinical benefit, and objective response for site evaluation and training purposes.

PROTOCOL SCHEMA

Figure 1. Proposed study procedure and timeline



1. Laboratory studies to include CBC, total bllirubin, SGOT [AST] , Creatinine,
2. To be evaluated prior to each treatment cycle

ABBREVIATIONS LIST

ABV	adriamycin, bleomycin, and vincristine
AE	adverse event
AERS	Adverse Event Reporting System
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AMC	AIDS Malignancy Consortium
AML	acute myelocytic leukemia
ANC	absolute neutrophil count
ART	antiretroviral therapy
AST	aspartate aminotransferase
BIP	bleomycin-induced pneumonitis
BMC	Bugando Medical Centre
BV	bleomycin and vincristine sulfate
cART	combined antiretroviral therapy
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
COPD	chronic obstructive pulmonary disease
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trials Monitoring Service
CXR	chest x-ray
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FACT-G	Functional Assessment of Cancer Therapy-General
FCBP	female of childbearing potential
FDA	Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
HAART	highly active antiretroviral therapy
HHV-8	human herpesvirus-8
HIV	human immunodeficiency virus

ICH	International Conference on Harmonisation
IDB	Investigational Drug Branch
IEC	institutional ethics committee
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
KPS	Karnofsky performance status
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma-associated herpesvirus
LFT	liver function test
LLN	lower limit of normal
MDS	myelodysplastic syndrome
MOP	manual of procedures
NCI	National Cancer Institute
NIMR	National Institute for Medical Research
NRTI	nucleoside reverse transcriptase inhibitor
ODMC	Operations and Data Management Center
OHAM	Office of HIV and AIDS Malignancy
OTC	over the counter
PCP	*Pneumocystis jirovecii* pneumonia
PD	progressive disease
PI	principal investigator
PIO	Protocol Information Office
PLD	pegylated liposomal doxorubicin
PN	peripheral neuropathy
PR	partial response
prn	pro re nata (as needed)
QOL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	System Organ Class
ULN	upper limit of normal
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objective

To evaluate the longitudinal quality of life of participants with HIV-associated KS during treatment with bleomycin and vincristine at a single institution in East Africa.

1.2 Secondary Objective

To explore baseline and time-dependent correlates of improvements in quality of life (QOL).

1.3 Exploratory Objective

To assess quality control (completeness and accuracy) in data capture of adverse events, clinical benefit, and objective response for site evaluation and training purposes.

2.0 BACKGROUND

2.1 Study Disease

Kaposi sarcoma (KS) is a vascular inflammatory tumor of endothelial origin caused by Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8).[1] HIV infection and immunosuppression dramatically increase the risk of KS among people infected with KSHV.

KS is the most common malignancy seen in patients with human immunodeficiency virus infection. The incidence of HIV associated KS remains high in parts of Africa where rates of both HIV and HHV-8 infection are high, but treatment options are often limited. In high resource countries, treatment for advanced AIDS-associated KS, in addition to antiretroviral treatment, typically includes chemotherapy.[2-8] While chemotherapy has been shown to reduce the burden of disease, it has not been shown to alter survival outcomes. The goal of treatment is palliation and improvement in quality of life (QOL). However, in low resource countries, such as Tanzania, the optimal treatment and the effect of treatment on quality of life is unknown.

2.2 Treatment Regimen

2.2.1 Bleomycin and vincristine

This study will only use standard of care drugs for the treatment of KS. The selection of bleomycin and vincristine sulfate (BV), and its choice over another regimen available in Tanzania, adriamycin, bleomycin, and vincristine (ABV), was based on several considerations. First, the large, randomized, controlled trials of liposomal anthracyclines versus BV or ABV were all conducted pre-highly active antiretroviral therapy (HAART). For example, in the randomized trial that compared pegylated liposomal doxorubicin (PLD) and BV reported by Stewart *et al.*, only half of the patients in each arm of the study were receiving any antiretroviral therapy (ART), and ART was confined to single or combination nucleoside reverse transcriptase inhibitors (NRTIs).[2]

In studies that have used rigorous response criteria, there was no evidence that BV was inferior to ABV with respect to objective, strictly defined response rates.[2-4] On the other hand, there was good evidence that BV had a superior toxicity profile compared to ABV, which was associated with a higher rate of hematologic toxicity and treatment delays for neutropenia and infection and also presents the risk of serious cardiotoxicity. In addition, as noted by Stewart *et al.,*[2] BV was also associated with considerably less myelosuppression than PLD, which may be particularly important in locales where hematopoietic growth factors like granulocyte-colony stimulating factor (G-CSF) are not available and where access to blood component transfusion is limited.

2.3 Study Design and Rationale

HIV seroprevalence among Tanzanians age 15-49 is estimated at 5.1%,[9] resulting in approximately 2.2 million HIV-positive persons within the country. Little is known about either the rate of objective response of KS to standard chemotherapy in this setting or its influence on QOL. Bugando Medical Centre (BMC) is a provisional AMC site and the current proposal is exploratory and intended to develop clinical research and database

management capacity. Additionally, knowledge of both the objective response rate to the current standard therapy and its influence on QOL, using a standardized questionnaire validated in Swahili, would be useful before embarking on clinical trials of other treatments for KS conducted with the AMC.

This is a prospective observational study to evaluate the quality of life of participants receiving BV for HIV-associated KS at a single institution in Tanzania. All participants presenting for care of HIV-associated KS at BMC during a 1-year study period will be approached for enrollment.

At enrollment, KS stage, clinical symptoms, CD4 count, complete blood count (CBC), liver, and renal function labs, and history of opportunistic infection will be recorded. The extent of KS will be evaluated at baseline and after each cycle of treatment, and response assessed using standard AMC criteria. The Functional Assessment of Cancer Therapy-General (FACT-G) QOL questionnaire has been used successfully in HIV-associated clinical trials to collect data in 4 categories: physical, emotional, functional, and social wellbeing. A Swahili version has been validated and will be used in the current proposal.[5] This questionnaire will be completed at four time points: prior to initiating treatment, after 3 cycles, at the end of therapy, and 3 months off therapy.

Participants will receive institutional standard of care treatment with BV, administered on day one of each 21-day chemotherapy cycle. Vincristine sulfate will be administered at a dose of 2 mg (fixed dose) over 1 minute into the sidearm of a rapidly flowing intravenous infusion every 3 weeks. The vincristine infusion will be followed by bleomycin administered at a dose of 15 units/m^2 over 10 minutes every 3 weeks.

Treatment with BV will continue for six cycles or until toxicity requiring discontinuation of chemotherapy, or the local physician determines that alternative therapy is required, whichever occurs first.

Institutional standard pre-treatment staging evaluation includes chest X-ray and physical history and exam. Complete blood cell counts, and serum liver/ renal function analysis will be required at each pretreatment visit. Other clinical or laboratory evaluations will be performed as deemed necessary by the medical provider. Clinical benefit, objective tumor response, and toxicity will be assessed every 3 weeks, prior to initiating each new chemotherapy cycle.

3.0 PARTICIPANT SELECTION

A CTEP-registered investigator (Dr. Nestory Masalu or Dr. Kristin Schroeder) will document that each protocol participant meets all stated eligibility criteria. Satisfaction of eligibility requirement will be documented prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

NOTE: Institutions may use this section of the protocol as an eligibility checklist for source documentation if it has been reviewed, signed, and dated before registration/randomization by the study investigator. If used as source documentation, this checklist must be printed, the investigator must check each item to document their assessment that the participant meets each eligibility criterion, and the completed checklist must be maintained in the participant's chart.

Participant ID Number: S007- ___ ___ ___ - ___ ___ ___ ___ ___

Patient's Initials (L, F, M): ___ ___ ___

3.1 Eligibility Criteria

____ 3.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term "licensed" refers to a U.S. FDA-approved kit or for sites located in countries other than the U.S., a kit that has been certified or licensed by an oversight body within that country and validated internally.

World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 ribonucleic acid (RNA) viral load.

____ 3.1.2 Participants must have pathologically confirmed Kaposi sarcoma.

____ 3.1.3 Participants should not have had prior therapy for their Kaposi sarcoma.

____ 3.1.4 All participants must be on stable antiretroviral therapy (ART) for a minimum of 12 weeks prior to study entry with an acceptable regimen that adheres to national guidelines for treatment of HIV infection.

____ 3.1.5 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of BV in participants <18 years of age, children are excluded from this study.

____ 3.1.6 ECOG performance status ≤ 2 (Karnofsky performance status ≥ 50%, see Appendix II).

____ 3.1.7 Participants must have organ and marrow function within the following parameters within 7 days of enrollment:

- Leukocytes: ≥ 3,000/mm^3
- Absolute neutrophil count: ≥ 1,000/mm^3
- Hemoglobin ≥ 8 g/dL
- Platelets: ≥ 75,000/mm^3
- Direct bilirubin: < 3mg/dL
- AST (SGOT) / ALT (SGPT): ≤ 2.5 X institutional upper limit of normal
- Creatinine:
  - Creatinine levels within normal institutional limits; or,
  - Creatinine clearance ≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal

____ 3.1.8 Participants with serious chronic, acute, or recurrent infections must have completed at least 14 days of therapy prior to enrollment and be clinically stable.

____ 3.1.9 If the participant is a female of childbearing potential (FCBP), defined as a sexually mature woman who: (1) has not undergone a hysterectomy or bilateral oophorectomy, or (2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months), the participant must have a negative urine or serum pregnancy test within 1 week prior to enrollment and agree to use an effective form of contraception (e.g., barrier contraception or hormonal contraception), during the 5 months of planned chemotherapy treatment and for 6 months after completing treatment.

____ 3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally, the presence of any of the following conditions will exclude a participant from study enrollment:

____ 3.2.1 Participants who are receiving any other investigational agents.

____ 3.2.2 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

____ 3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bleomycin or vincristine.

____ 3.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

____ 3.2.5 Participants who are breastfeeding a child. Because there is an unknown but

potential risk for adverse events in nursing infants secondary to treatment of the mother with BV, breastfeeding should be discontinued if the mother is treated with this chemotherapy.

____ 3.2.6 Current or history of known pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), emphysema, bronchiectasis, or diffuse or significant local radiographic interstitial infiltrates on chest x-ray (CXR) or computed axial tomography (CT) scan, that, in the opinion of the investigator, would exclude bleomycin use.

NOTE: Participants with an abnormal CXR or CT scan (which may indicate pulmonary KS) should undergo screening evaluations **to rule out an infectious cause, per standard of care. If available, other diagnostic procedures such as bronchoscopy should be considered to confirm the presence or absence of pulmonary KS and/or an infectious agent. These procedures should be completed outside the study.** These participants should be excluded if, in the opinion of the site investigator, use of bleomycin would be detrimental.

____ 3.2.7 Oxygen saturation less than 90% and/or exercise desaturation greater than 4% within 14 days before study enrollment.

NOTE: Exercise is defined as any activity that will increase a participant's resting heart rate by at least 20 beats/minute.

3.3 Number of Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll up to 20 participants.

3.3.2 Accrual rate

Approximately 2 participants per month.

3.4 Participant Enrollment Procedures

This protocol must be approved by the Institutional Review Board (IRB), the National Institute for Medical Research (NIMR) in Tanzania, and the participating site must be registered for study participation with the AMC Operations and Data Management Center (ODMC) before participant enrollment.

After it has been determined that the participant is eligible and an informed consent form has been signed by the participant, the participant must be registered on-line via the AMC Internet Data Entry System (Advantage eClinical). Enrollment and data collection will occur via Advantage eClinical.

The participating site will ensure a participant meets all eligibility criteria prior to completing the protocol-specific eligibility checklist in Advantage eClinical for enrollment. Participants will be enrolled on-line via Advantage eClinical no more than 1 week prior to the initiation of treatment (enrollment 1 day prior to or on the day of treatment is strongly encouraged). Once the eligibility checklist is submitted a system-generated confirmation email will be sent to the enroller upon successful completion of the participant enrollment. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amipm@emmes.com or via phone at 301-251-1161) for further instructions.

4.0 TREATMENT PLAN

The treatment plan (Section 4.0) and dose modifications (Section 5.0) and clinical and laboratory evaluations (Section 8.0) presented in this protocol represent the standard of care for KS treatment at Bugando Medical Centre. As the primary aim of this investigation is to assess quality of life, this treatment plan represents the general guidelines the site will follow for patient care concurrent to survey assessments required by this protocol. Excepting cases where enrolled participants do not receive any doses of standard of care chemotherapy and therefore cannot be assessed for the effect of treatment on quality of life, adherence to the treatment plan will not be assessed for this protocol.

4.1 Treatment Administration

Standard treatment will be administered on an outpatient basis. Reported adverse events and potential risks for bleomycin and vincristine are described in Section 6.0. Appropriate dose modifications for bleomycin and vincristine are described in Section 5.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Table 4-A: Treatment Administration

Drug	Dose	Route	Schedule
Vincristine sulfate (V)	2 mg in 2mL (undiluted)	IV over 1 minute **(maximum 2 minutes)**	Every 21 days for up to six cycles
Bleomycin sulfate (B)	15 units/m^2 in 50 mL 0.9% sodium chloride for injection	IV over 10 minutes	Every 21 days for up to six cycles

4.1.1 Standard therapy dosing instructions

BV will be administered on day 1 of each 21-day cycle.

Each cycle of BV should be administered 21 days (±2 days) after the first day of the previous cycle. BV must not be administered earlier than 19 days after the previous cycle.

Treatment with BV will continue for six cycles, or until toxicity requiring discontinuation of study chemotherapy, or the site investigator has determined that alternative therapy is required, whichever occurs first.

4.1.1.1 Vincristine sulfate will be administered at a dose of 2 mg (fixed dose) in a volume of 2 mL over 1 minute into the sidearm of a rapidly flowing intravenous infusion every 21 days (±2 days) (see Section 5.2.2 for specific instructions regarding dosage reduction for participants with elevated bilirubin). The vincristine infusion will be followed by bleomycin as detailed below.

4.1.1.2 Vincristine should be administered before bleomycin if given in the same IV line.

4.1.1.3 Bleomycin sulfate will be administered at a dose of 15 units/m^2 over 10 minutes every 21 days (±2 days) (see Section 5.3 for specific instructions

regarding dosage reduction for participants whose creatinine clearance falls below 60 mL/min).

Maximum cumulative lifetime total dose of bleomycin is 400 units.

4.1.2 See Section 5.0 for specific instructions regarding dosage modification for participants.

4.2 Concomitant Medication and Supportive Care Guidelines

4.2.1 General

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the participant, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate, are allowed.

Warfarin/coumarin anticoagulants: Avoid if possible. Use often causes an elevation or fluctuation in the INR. In the first instance consider switching participant to a low molecular weight heparin during treatment or if the participant continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

The administration of any other therapies intended to treat KS including chemotherapy and biologic agents is NOT permitted. The use of other concurrent investigational drugs is not allowed.

The following categories of concurrent medications will be recorded in AdvantageEDC:

- All antiretroviral drugs
- Anti-infective drugs
- Hematopoietic colony stimulating factors
- Any drugs used to treat KS symptoms (e.g., analgesics) or treatment-related adverse events.
- Any disallowed medications

4.2.2 Bleomycin

Mucositis

Skin and mucosal changes are the most frequent side effects, occurring in approximately 50% of treated patients and are dose-related. Topical steroids may be useful. Skin ulceration and/or peeling on fingertips may be painful and can require discontinuation of bleomycin.

Skin Pigmentation

Bleomycin can cause unusual pigmentation on the trunk consisting of linear streaks with crisscross patterns in 8-20% of patients.

Fever

Fever and chills occur in approximately 50% of patients. These reactions usually occur starting a few hours after treatment, and may last up to 4-12 hours. Pre-treatment with hydrocortisone 100 mg IV significantly decreases severity of the

reaction. Acetaminophen q3-4h prn can be used to control fever if it occurs.

4.2.3 Vincristine

Peripheral neuropathy

Neurotoxicity is dose- and exposure-related, with increased toxicity in prolonged infusion. Neurotoxicity is generally reversible, but recovery may be slow. The most frequent manifestation of nervous system toxicity is peripheral neuropathy, the earliest indication of which is the depression of the Achilles reflex. Later loss of other deep tendon reflexes occurs and is accompanied by peripheral paresthesias, pain, and tingling. Cranial nerve neuropathy may lead to vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain. Treatment of neuropathy symptoms may be offered as available in line with local standard of care. If a participant is receiving an ART drug associated with peripheral neuropathy (PN), stopping that particular drug and switching to an alternative nucleoside reverse transcriptase inhibitor (NRTI) is recommended, where available.

Severe jaw pain can occur within a few hours of the first dose of vincristine, and can be treated with acetaminophen or pain medications.

Constipation

Constipation (which can be severe) is due to autonomic neuropathy, presenting as abdominal pain, urinary retention and paralytic ileus. Laxatives or stool softeners should be given routinely to prevent constipation. These symptoms resolve with time and may not occur with subsequent treatment.

4.2.4 Other

Infectious and disease related complications will be managed per institutional protocol per primary HIV care team.

4.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 6 cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator
- Participant non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual

period) at any time during study participation.

- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a participant in the study.

- Termination of the study by sponsor.
- The drug manufacturer(s) no longer manufacture the drugs.

4.4 Duration of Follow Up

All participants will be followed for 12 weeks after removal from protocol treatment or until death, whichever occurs first. Participants who discontinue study participation will be able to continue prescribed chemotherapy off protocol per institutional standard of care.

5.0 DOSING DELAYS/DOSE MODIFICATIONS

Except as noted below, if an adverse event requiring a delay in chemotherapy does not recover to the level required for continued chemotherapy treatment within 3 weeks of the scheduled date of the next cycle (i.e., within 42 days after the start of the previous cycle), chemotherapy should be discontinued.

In any case in which the dose of prescribed chemotherapy is reduced due to toxicity, any future dosing (for that cycle and all subsequent cycles) should be at the reduced dose unless otherwise noted.

5.1 Dose Modifications for BV

Table 5-A: Dose Modifications for BV - Nausea

Event Name	Nausea
Grade of Event	Management/Next Dose
≤ Grade 1	No change in next dose.
Grade 2	No change in next dose. Increase supportive antiemetics.
Grade 3/4	Delay start of cycle * until < Grade 2. Increase supportive antiemetics.
*Participants requiring a delay of >2 weeks should go off protocol therapy. Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Table 5-B: Dose Modifications for BV - Vomiting

Event Name	Vomiting
Grade of Event	Management/Next Dose
≤ Grade 1	No change in next dose
Grade 2	No change in next dose. Increase supportive antiemetics
Grade 3	Delay start of cycle* until < Grade 2. Increase supportive antiemetics
Grade 4	Off protocol therapy
*Participants requiring a delay of > 2 weeks should go off protocol therapy. Participants requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Table 5-C: Dose Modifications for BV - Anemia

Event Name	Anemia
Grade of Event	Management/Next Dose
≤ Grade 1 (LLN - 10g/dL)	No change in next dose
Grade 2 (< 10 - 8.0 g/dL)	No change in next dose
Grade 3 – 4 (< 8 g/dL)	Red blood cell transfusion is recommended to increase the hemoglobin level to ≥ 8.0 g/dL. Chemotherapy can continue for hemoglobin < 8.0 – 6.5 g/dL. For hemoglobin < 6.5 g/dL, chemotherapy should be held and the participant transfused with red blood cells until the hemoglobin level has returned to ≥ 8.0 g/dL. Study medication may then be resumed at full dose. If hemoglobin < 6.5 g/dL recurs after resumption of chemotherapy, the participant should again be transfused as above. Chemotherapy may then be resumed as follows: 25% reduction in the dose of both drugs.
Participants requiring > two dose reductions should go off protocol therapy.	

Table 5-D: Dose Modifications for BV - Neutropenia

Event Name	Neutropenia
Grade of Event	Management/Next Dose
≤ Grade 1 (LLN-1500/mm^3)	No change in next dose
Grade 2 (< 1500-1000/mm^3)	No change in next dose
Grade 3 (< 1000-500/mm^3)	Delay start of cycle * until < Grade 3. No change in next dose. If delayed a second time, decrease bleomycin by 25%. **
Grade 4 (< 500/mm^3)	Delay start of cycle * until < Grade 3. Resume but decrease bleomycin dose 25%. ***
*Participants requiring a delay of > 2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy. *** Febrile neutropenia: ANC < $0.5x10^9$/L plus fever requiring hospitalization, reduce dose to 11mg/m^2 for all future BV therapy.	

Table 5-E: Dose Modifications for BV - Thrombocytopenia

Event Name	Thrombocytopenia
Grade of Event	Management/Next Dose
≤ Grade 1 (LLN-75,000/mm3)	No change in next dose
Grade 2 (< 75,000-50,000/mm3	No change in next dose
Grade 3 (< 50,000-25,000/mm3)	Delay start of cycle * until > 50,000. Resume at 50% dosing of bleomycin.
Grade 4 (< 25,000)	Delay start of cycle * until < Grade 2. Resume at 50% dosing of bleomycin. **
*Participants requiring a delay of > 2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.	

5.2 Dose Modifications for Vincristine

5.2.1 Peripheral neuropathy

Table 5-F: Dose Modifications for Vincristine – Peripheral Neuropathy

Event Name	Peripheral Neuropathy
Grade of Event	Management/Next Dose
Grade 1-2	No change in next dose. Treatment of neuropathy symptoms may be offered as available in line with local standard of care. If a participant is receiving an ART drug associated with peripheral neuropathy (PN), stopping that particular drug and switching to an alternative nucleoside reverse transcriptase inhibitor (NRTI) is recommended, where available.
Grade 3-4	Discontinue vincristine. Symptomatic treatments to treat neuropathy symptoms may be offered as available in line with local standard of care.

Table 5-G: Dose Modifications for Vincristine – Constipation or Ileus

Event Name	Constipation or Ileus
Grade of Event	Management/Next Dose
Grade 1-2	No change in next dose. Treatment of constipation symptoms may be offered as available in line with local standard of care.
Grade 3-4	Hold dose; institute aggressive regimen to treat constipation if present. When symptoms reduce to ≤ grade 3 resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.
Participants requiring > two dose reductions should go off protocol therapy.	

5.2.2 Elevated total bilirubin

Table 5-H: Elevated Total Bilirubin

Event Name	Elevated Total Bilirubin
Grade of Event	Management/Next Dose for Vincristine
Grade 1	No change in next dose
Grade 2	50 % dosing of baseline dose of vincristine*
Grade 3	25% dosing of baseline dose of vincristine*
Grade 4	Off protocol therapy
* If bilirubin within normal range after reduced dose, may rechallenge with next dose increment for subsequent cycle.	

5.3 Dose Modifications for Bleomycin

5.3.1 Pulmonary toxicity

Participants with bleomycin induced pneumonitis (BIP) present initially with a nonproductive cough, exertional dyspnea, and sometimes fever. Participants should be questioned carefully for new dry unproductive cough or new respiratory limitation of exercise tolerance at each visit. Persistence of either of these symptoms for longer than one week without other explanation, such as infection, should prompt consideration of BIP. A normal chest x-ray is unreliable to exclude BIP. Evaluate for infectious causes per institutional standard and consider antibiotic use if appropriate. If infections are excluded, the administration of corticosteroids is indicated.

Table 5-I: Dose Modifications for Bleomycin – Pulmonary Toxicity

Event Name	Pulmonary Toxicity
Grade of Event	Management/Next Dose
Grade 1-2	Hold and investigate*. If confirmed treat with corticosteroids. If a greater than 4% decrease in oxygen saturation develops or persists after treatment of an intercurrent infection, such as *Pneumocystis jirovecii* pneumonia (PCP), then bleomycin will be permanently discontinued.
Grade 3	Decrease subsequent dose to 75%. If a greater than 4% decrease in oxygen saturation develops or persists after treatment of an intercurrent infection, such as *Pneumocystis jirovecii* pneumonia (PCP), then bleomycin will be permanently discontinued.
Grade 4	Discontinue.
* Duration of hold must not exceed 21 days after scheduled dose	

5.3.2 Renal Insufficiency

Table 5-J: Dose Modifications for Bleomycin – Renal Insufficiency

Event Name	Renal Insufficiency
Creatinine clearance (mL/min)	Percent of baseline bleomycin dose
>/= 50	**100%**
40 – 50	**70%**
30 – 40	**60%**
20 – 30	**55%**
10 – 20	**45%**
5 – 10	**40%**

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting **in addition** to routine reporting (via Advantage eClinical). All adverse event reporting will be conducted via Advantage eClinical for this protocol.

The CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5.0 of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Version 5.0 of CTCAE.

6.1 Adverse Events and Potential Risks Lists

For full details, consult the package insert.

Table 6-A: Adverse Event List for Vincristine

Rare or Serious Side Effects	Frequently Occurring Side Effects
Autonomic neuropathy	Nausea and vomiting (minimal)
Bronchospasm	Alopecia (reversible)
Seizure	Constipation
Insomnia	Myelosuppression (mild)
Cranial Neuropathy	Musculoskeletal pain
SIADH	Peripheral Neuropathy
Chemical Phlebitis	
Acute Hypersensitivity reactions	
Hypertension	

Table 6-B: Adverse Event List for Bleomycin

Rare or Serious Side Effects	Frequently Occurring Side Effects
Hypotension	Nausea and vomiting (minimal)
Pleuropericarditis	Alopecia (reversible)
Radiation recall reaction	Nail changes
Disseminated intravascular coagulation	Pruritus
Hemolytic uremic syndrome	Skin hyperpigmentation
Pneumonitis	Mucositis (30%)
	Fever, chills

6.2 Classification of AEs by Severity and Relationship to Treatment Administration

6.2.1 Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible,

probable, or definite).

This includes the following:

- AEs not previously observed in the participant that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the study disease that were not present prior to study entry.
- Complications that occur as a result of protocol interventions.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency, or changed in character during the protocol-specified AE reporting period.

AEs will be followed for the participant's medical care until resolved to the baseline condition or protocol completion; for chronic conditions, resolution may occur when the AE is stable with appropriate medical management.

6.2.2 Life-threatening adverse event: Any AE that places the participant or participant, in view of the Investigator, at immediate risk of death from the reaction.

6.2.3 Serious adverse event (SAE): Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.2.4 Hospitalization: hospitalization for expedited AE reporting purposes is defined as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the AE and should **ONLY** be used for situations where the AE truly fits this definition and **NOT** for hospitalizations associated with less serious events. (*e.g.*, a hospital visit where a patient is admitted for observation or minor treatment such as, hydration and released in less than 24 hours).

Prolongation of hospitalization is defined as an extension of current hospitalization equal to or greater than 24 hours.

Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

6.2.5 Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term 'toxicity' because of familiarity.

6.2.6 Unexpected adverse event: Any AE that is not listed in available sources including

the package insert, the Investigator's Brochure, or the protocol, or is not consistent with the severity or specificity of the risk information described in the available sources, or is not consistent with the severity or specificity of the risk information described in the available sources.

6.2.7 CTEP Adverse Event Reporting System (CTEP-AERS): An electronic system for expedited submission of AE reports. A SAE reporting form in Advantage eClinical will be used in lieu of CTEP-AERS for expedited AE reporting on this trial.

6.2.8 Attribution: An assessment of the relationship between the AE and the medical intervention. The CTCAE does not define an AE as necessarily "*caused by a therapeutic intervention."* After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Table 6-C: Attribution

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to treatment/intervention	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to treatment/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

NOTE: AEs listed as 'possibly, probably, or definitely' related to the treatment/intervention are considered to have a suspected 'reasonable causal relationship' to the treatment/intervention (ICH E2A). For routine adverse event reporting purposes on this protocol, "attribution" defines the relationship between the adverse event and the treatment/intervention.

6.3 Expedited Adverse Event Reporting

6.3.1 Expedited AE reporting for this study must use Advantage eClinical. The reporting procedures to be followed are presented in this section and will align with the principles for SAE reporting in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements," which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined below (Section 6.3.3).

A 24-hour notification is to be made to the AMC ODMC by telephone at +1 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into Advantage eClinical by the original submitter at the site.

6.3.2 Advantage eClinical is programmed for automatic electronic distribution of SAE reports to the following individuals: the AMC ODMC, AMC Medical Monitor, Protocol Chairs, and the Principal Investigator at the institution.

6.3.3 Expedited reporting guidelines

Investigators must report ALL SAEs (as defined in Section 6.2.3) that occur from enrollment through 30 days following protocol treatment discontinuation to the AMC and IRBs as required. The investigator's initial report to the AMC will be made using the Adverse Event form in Advantage eClinical within 24 hours of awareness of the event, followed by a completed SAE form within the following timelines.

- Grade 3 SAEs: complete SAE form within 10 calendar days of investigator awareness
- Grade 4 or 5 SAEs: complete SAE form within 5 calendar days of investigator awareness

After 30 days following treatment discontinuation, SAEs will only be reported in the SAE form if determined by the investigator to have an attribution to treatment of possible, probable, or definite.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions – Disease Progression."** Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

6.3.4 Expedited reporting for pregnancy

Female participants who become pregnant or initiate breastfeeding while on protocol treatment must immediately discontinue protocol treatment. Participants will continue to be followed for the remainder of the study visit schedule and procedures. AMC-S007 will not provide perinatal care for women. Women who become pregnant will be referred to local clinics and/or other research studies for prenatal and postpartum care.

Pregnancy reporting and outcomes will be documented by completion of the appropriate CRFs, including the Adverse Event form, using the appropriate term in the system organ class (SOC) for Pregnancy, puerperium and perinatal conditions.

6.3.5 Expedited reporting to regulatory authorities

The principal investigator is responsible for ensuring that any AE or SAE that requires reporting to its IRB or respective national regulatory authority is completed in accordance with legal and regulatory timelines.

As this trial will not be conducted in the U.S., and will not support a marketing application or change in labeling or advertising for the drug, the trial is exempt from the requirement for an IND. No serious adverse event reporting to FDA is required.

6.4 Routine Adverse Event Reporting

With the exception of the cases noted below, selected adverse events that occur within

timeframes defined in protocol Section 6.4.3 **must** be reported in routine study data submissions.

6.4.1 Additional protocol-specific routine adverse event reporting exclusions

All grade 1 adverse events are not required to be reported in the Adverse Event Form in Advantage eClinical. These adverse events must be recorded in the source documents only.

6.4.2 Timeline for routine adverse event reporting

AEs will be recorded in the source and assessed for routine reporting requirements from receipt of the first dose of BV through the treatment discontinuation evaluation. Following treatment discontinuation, only SAEs that are possibly, probably, or definitely attributed to treatment, or grade 5 SAEs will be reported in the AE form.

6.5 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with an agent/intervention, radiation, or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with standard treatment on this protocol will be reported expeditiously via Advantage eClinical. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

6.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine adverse event reporting.

7.0 PHARMACEUTICAL INFORMATION

No medications will be provided by the study. The site will source medications from its usual commercial pharmacy per institutional policy, and administer these drugs in accordance with the approved package inserts.

7.1 Study Product Preparation

7.1.1 Bleomycin

Description

Bleomycin is an antibiotic complex produced by fermentation from *Streptomyces verticillus*. It causes single- and double-strand DNA breaks through formation of an intermediate iron complex. DNA synthesis, and to a lesser degree, RNA and protein synthesis are inhibited. Bleomycin is cell cycle phase-specific. Please refer to the approved package insert for complete prescribing and toxicity information.

Reconstitution of Lyophilized Product

The locally-available formulations of bleomycin are packaged as 15 units of bleomycin sulphate powder per vial. Instructions for reconstitution described for the Zuvius Lifescience product should be followed: Zuvius's formulation of bleomycin is packaged as 15 units of bleomycin sulphate powder per vial. Using aseptic technique, reconstitute each vial with 5 mL of 0.9% sodium chloride for injection to yield 3 Units/mL (15 Units/ 5 mL) solution. If these reconstitution and preparation instructions are not in accordance with the package insert of the locally-sourced bleomycin, then the site should must the package insert and proposed preparation instructions to the protocol team for review and approval prior to use.

Withdraw study participant's calculated dose of bleomycin in mL from the reconstituted bleomycin vial(s) into a syringe and inject it into a 50 mL 0.9% sodium chloride for injection IV bag.

Administer the prepared bleomycin in 50 mL 0.9% sodium chloride for injection IV bag by IV infusion over 10 minutes.

Bleomycin prepared in 50 mL 0.9% sodium chloride IV bag for infusion should be stored as directed by the manufacturer in the package insert.

Do not use if a precipitate, foreign matter, or discoloration is present.

Bleomycin for injection should not be reconstituted or diluted with 5% dextrose for injection or other dextrose-containing diluents, as loss of potency can occur.

Do not mix bleomycin with other drugs or solutions, as compatibility is unknown.

Caution should be exercised in handling bleomycin. The use of gloves and gown is recommended. If bleomycin comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.

Administration

Reconstitute with 5-10mL normal saline.

May be given by direct IV push over 10 minutes, followed by a saline flush, if no IV line has been set up. Or may further dilute in 100mL normal saline and infuse over 10-15 minutes.

7.1.2 Vincristine sulfate

Description

Vincristine sulfate is a vinca alkaloid from the plant Cantharanthus roseus. It acts by binding to or crystallizing microtubular proteins of the mitotic spindle. It is a cell cycle phase -specific drug and can also affect DNA directed RNA polymerase. It has a triphasic half-life and primary elimination is by the liver into the bile and feces. Please refer to the approved package insert for complete prescribing and toxicity information.

Drug Preparation and Administration

Using aseptic technique, withdraw 2 mL from vial(s) of vincristine containing 2mg/2mL (or 1mg/1mL) into a syringe and cap.

Vincristine prepared in a syringe should be administered as soon as prepared.

Do not use if a precipitate, foreign matter or discoloration is present.

Caution should be exercised in handling vincristine. The use of gloves and gown is recommended. If vincristine comes in contact with the skin or mucosa, immediately wash thoroughly with soap and water.

Do not mix vincristine with other drugs or solutions, as compatibility is unknown.

Include on the prepared vincristine study product label "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE ONLY."

Administer IV over 1 minute (see Section 4.1 for note regarding acceptable IV infusion times).

Vincristine must be administered via an intact free-flowing intravenous needle or into the tubing of a running intravenous infusion and then flushed with the IV fluid being administered. Care should be taken that no leakage or swelling occurs during administration. If any leakage or swelling occurs during administration, the injection should be discontinued immediately and any remaining portion of the dose should then be introduced into another vein.

Vincristine should be administered before bleomycin if given in the same IV line.

7.1.3 Handling and disposal

Bleomycin should not be mixed with other drugs until specific compatibility data are available. The presence of any bacteriostatic agent, such as benzyl alcohol, may cause precipitation of bleomycin and vincristine.

Caution should be exercised in handling bleomycin and vincristine solutions. The use of gloves is recommended. If bleomycin or vincristine comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

Bleomycin and vincristine should be handled and disposed of in a manner consistent with other anti-cancer drugs.

7.2 Drug Accountability

Drug accountability will be managed according to local policy.

8.0 CLINICAL AND LABORATORY EVALUATIONS

Schedules shown in the Study Calendar below are provided in Appendix I.

8.1 Screening/Baseline Evaluations

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy, unless otherwise specified below. Scans and X-rays must be done within two weeks prior to the start of therapy.

8.1.1 Medical history

8.1.2 Medication history, including current ART and prior ART regimens in last year. Additional dietary supplements, over-the-counter (OTC) medications or traditional medications taken within the previous 3 months should also be recorded.

8.1.3 Physical examination including vitals, height, weight, and performance status

8.1.4 Pre-treatment staging evaluation includes chest X-ray

8.1.5 Complete blood cell counts with differentials and platelets, and serum liver/renal function analysis. This should include the following: total and direct bilirubin, creatinine, SGOT [AST], SGPT [ALT].

8.1.6 Oxygen saturation levels (within 14 days before study enrollment)

8.1.7 Biopsy diagnostic of KS at any time prior to study enrollment

8.1.8 Tumor measurements

8.1.9 Serum or urine pregnancy test for women of childbearing potential

8.2 Evaluations during Treatment

Other clinical or laboratory evaluations will be performed as deemed necessary by the medical provider. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 24 hours prior to initiation of the next cycle of therapy. All evaluations may be performed up to 48 hours prior to scheduled treatment unless otherwise stated.

8.2.1 Toxicity evaluation at every visit. Physical examination with vitals and performance status to be performed at every visit, with weight captured at cycles 3 and 5.

8.2.2 Complete blood cell counts with differentials and platelets, and serum liver/renal function analysis will be required at each pretreatment visit, up to three days prior to receiving chemotherapy. See the list of required tests in Section 8.1.5.

8.2.3 Serum or urine pregnancy test for women of childbearing potential will be completed prior to each cycle.

8.2.4 Oxygen saturation levels will be required at each pretreatment visit, up to three days prior to receiving chemotherapy.

8.2.5 Objective tumor response, toxicity, and clinical benefits will be assessed every 3 weeks, up to three days prior to initiating next chemotherapy cycle.

8.2.6 Trained site personnel will administer the quality of life questionnaire (FACT-G,

Appendix IV) at 4 time points: prior to initiating treatment, cycle 4 prior to chemotherapy, completion of treatment and final study visit. Results recorded on the CRFs. Trained site personnel are defined as site pharmacist, nursing staff, clinician, or other trained clinical personnel (e.g., adherence counselors, social workers). It is estimated that this assessment will take 10-15 minutes to complete.

8.3 Treatment Discontinuation Evaluations

8.3.1 All participants will have the following evaluations and laboratory tests within three weeks of the last dose of protocol treatment, regardless of the reason for discontinuation:

- Physical examination including vitals, weight, and performance status
- Toxicity evaluation
- Tumor response evaluation, including radiologic evaluation for participants that had visceral KS at baseline or those who have symptoms suggestive of visceral KS at treatment discontinuation
- CBC with differentials and platelets
- Liver and renal function labs as defined in Section 8.1.5
- Oxygen saturation level
- FACT-G questionnaire

8.4 Final Evaluations, Off Study

In addition to the evaluations listed below, the Off-Study Summary Form should be completed in Advantage eClinical.

8.4.1 All participants will have the following evaluations and laboratory tests within three months of the last dose of protocol treatment, regardless of the reason for discontinuation:

- Physical examination including vitals, weight, and performance status
- Toxicity evaluation
- Tumor response evaluation, including radiologic evaluation for participants that had visceral KS at baseline or those who have symptoms suggestive of visceral KS at treatment discontinuation
- CBC with differentials and platelets
- Liver and renal function labs as defined in Section 8.1.5
- Oxygen saturation level
- FACT-G questionnaire

9.0 MEASUREMENT OF EFFECT

All participants will be evaluated for KS response by physical examination as described in the AMC KS Tumor Assessment Manual of Procedures (MOP) within 3 days prior to the first day of every cycle. See Appendix I for the KS Tumor Assessment schedule.

9.1 Definition of Response

Response and progression will be evaluated in this study as follows:

9.1.1 Complete response (CR): CR is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. In some individuals, residual skin color changes may remain visible at one or more site(s) of lesions that were previously raised and/or red or violaceous. Suspected CR in those lesions refers only to residual macules (flat, non-palpable lesions) that are slightly darker than the surrounding normal skin. If such lesions are present in a participant otherwise believed to have a CR, biopsy of at least one such lesion is required in order to document the absence of malignant cells and to confirm CR. In the event that such a confirmatory biopsy is not performed and residual pigment persists, the response will be considered partial (PR). In participants in whom all detectable cutaneous disease has resolved and in whom there are no visible pigmented macules as described above, a confirmatory skin biopsy is not required. In participants known to have had visceral disease, an attempt at restaging with appropriate endoscopic or radiographic procedures should be made.

NOTE: To classify a response as a CR, the participant must have a CR in both the cutaneous and noncutaneous (if applicable) sites of disease and no evidence of progression as defined by the above criteria.

9.1.2 Partial response (PR): PR is defined as no new oral lesions or new or progressive visceral sites of involvement, or the appearance or worsening of tumor-associated edema (as defined in the MOP) or effusions or the development of five or more new cutaneous lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease; AND

- A 50% or greater decrease in the number of all lesions present at entry (either total body or in the representative areas) lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesions become macules, either total body or in the representative areas) present at entry lasting for at least 4 weeks; OR
- A 50% or greater decrease in the area of the cutaneous marker lesions compared with entry lasting for at least 4 weeks; OR
- A 50% or greater decrease in the number or size of all measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions; OR
- Complete disappearance of non-measurable oral or visceral lesions lasting for at least 4 weeks, without evidence for progression of cutaneous lesions.

NOTE: To classify a response as PR, the participant must have at least a PR in either the cutaneous or noncutaneous sites of disease, and no evidence of progression as defined in the above criteria.

NOTE: Participants with residual tumor-associated edema or effusion who otherwise meet the criteria for CR will be classified as having a PR.

9.1.3 Stable disease (SD) is defined as any response not meeting the criteria for CR, PR, or progressive disease.

9.1.4 Progressive disease (PD) is defined as follows:

For participants with ≤50 cutaneous lesions

PD is defined as any one or more of the following:

- ≥ 25% increase in the area of the cutaneous marker lesions compared to entry or best response;
- ≥ 25% increase in the total lesion count**,** or a minimum of five new lesions**,** whichever is greater, compared with entry or best response;
- ≥ 25% increase in the number of raised lesions, or a minimum of five new raised lesions, whichever is greater, compared with entry or best response.

NOTE: There are body sites where disease is particularly difficult to evaluate, and a few new lesions may be counted in spite of the fact that a participant is not actually progressing. For example, lesions of the foot, particularly those that are flat, are difficult to evaluate because their intensity may vary based on how much edema is present, how much the person walked the day before, how long his/her feet have been in a dependent position prior to the physical exam.

For participants with >50 cutaneous lesions

PD is defined as any one or more of the following:

- ≥ 25% increase in the area of the cutaneous marker lesions compared to entry or best response;
- ≥ 25% increase in the total number of lesions in the prospectively defined anatomic sites containing representative lesions;
- a total of five new lesions in anatomic sites that were previously documented as having no evidence of cutaneous disease,
- ≥ 25% increase in the number of raised lesions in the prospectively defined anatomic sites containing representative lesions (minimum of five raised lesions if there are very few raised lesions, for example < 8) whichever is greater. Photographic documentation of "gross" or significant progression, particularly in areas that were not being followed, will be of particular value.

9.1.5 Noncutaneous progression (PD): Noncutaneous PD includes new oral or visceral sites of involvement or progression of oral or visceral disease or the development of new or increasing tumor-associated edema or effusion that interferes with the participant's normal activities lasting for at least two consecutive evaluations.

Progressive oral or visceral disease, for measurable and evaluable disease, should be analogous to cutaneous KS response criteria.

Progressive edema is defined as the following:

- An increase in non-pitting/woody edema in an upper or lower extremity associated with an increase in limb circumference of at least 3 cm from entry or best response, sustained for at least two consecutive evaluations, and measured at a fixed point on the extremity with respect to a bony landmark (e.g., 10 cm below the lower border of the patella); AND/OR
- New appearance of non-pitting/woody edema in an extremity where none was previously present, sustained for at least two consecutive evaluations; AND/OR
- New or worsening edema in a non-extremity site (e.g., periorbital, genital) that interferes with function and is sustained for at least two consecutive evaluations.

9.1.6 Recurrent disease

Recurrent disease is defined as the appearance of tumor following documentation of a complete remission.

9.1.7 Time to response

Time to response is defined as time from the first dose of chemotherapy until documentation of first response.

9.1.8 Time to progression

Time to progression is defined as time from initiation of chemotherapy to documentation of first progression.

9.1.9 Response duration

Response duration is defined as the time from first documentation of response to documentation of first progression.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

This is a prospective observational study to evaluate the quality of life of patients receiving liposomal doxorubicin for HIV-associated Kaposi sarcoma and a single institution in Tanzania. The exploratory aim of this trial is to assess clinical data collection quality for site evaluation and training purposes only.

All patients presenting for care of HIV-associated KS at Bugando Medical Centre during a 1-year study period will be approached for enrollment.

10.2 Sample Size/Accrual Rate

We anticipate approximately 1-2 participant will be accrued each month, for a total of approximately 12 to 20 participants.

10.3 Statistical Analysis

We expect 1-2 participants per month during a 1-year enrollment for a total of 12-20 participants. With limited enrollment, statistics are exploratory only. QOL questionnaires will be collected prior to treatment, after 3 cycles, at treatment completion and 3 months after treatment completion. The four domains of the FACT-G questionnaire will be determined for each questionnaire: physical well-being, social/family well-being, emotional well-being and functional well-being. Using general estimating equations, we will explore changes in these domains with time. Logistic regression analyses will be used to correlate changes in quality of life domains with clinical response.

11.0 ROLE OF DATA MANAGEMENT

11.1 CRF Instructions

Access to the internet data entry system for this study, Advantage eClinical, and instructions for recording of study data on CRFs will be provided by the AMC ODMC at www.amcoperations.com. Participating institutions are responsible for submitting data and/or data forms via Advantage eClinical in accordance with the AMC Data Entry Guide and specific form instructions, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

11.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix III, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

11.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html). The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB/IEC, which specifically approves the protocol and informed consent, before participant enrollment. The IRB/IEC must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are participant to inspection during or after completion of the study. AEs must be reported to the IRB according to local procedures. The IRB should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature, significance and risks associated with the study must be explained to the participant. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the participant to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

12.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IRB/IEC of the treating institution. A copy of the written approval of the IRB/IEC and NIMR must be sent to the ODMC.

12.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective populations.

Table 12-A: Accrual Targets

INTERNATIONAL PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	10	10	0	0	20
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	10	10	0	0	20

13.0 REFERENCES

1. Ganem D. KSHV infection and the pathogenesis of Kaposi's sarcoma. Ann Rev Pathol 2006;1:273-96.
2. Stewart S, Jablonowski H, Goebel FD, et al: Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol 16:683-91, 1998
3. Gill PS, Miles SA, Mitsuyasu RT, et al: Phase I AIDS Clinical Trials Group (075) study of adriamycin, bleomycin and vincristine chemotherapy with zidovudine in the treatment of AIDS-related Kaposi's sarcoma. AIDS 8:1695-9, 1994
4. Northfelt DW, Dezube BJ, Thommes JA, et al: Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. J Clin Oncol 16:2445-51, 1998
5. Welles L, Saville MW, Lietzau J, et al. Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. J Clin Oncol 1998;16:1112-21.
6. Tulpule A, Groopman J, Saville MW, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. Cancer 2002; 95:147-154.
7. Stebbing J, Wildfire A, Portsmouth S, et al. Paclitaxel for anthracycline-resistant AIDS-related Kaposi's sarcoma: clinical and angiogenic correlations. Ann Oncol 2003; 14:1660-1666.
8. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi's sarcoma: Evidence for symptom palliation from chemotherapy. Cancer 2010;116(16):3969-77.
9. Tanzania Commission for AIDS (TACAIDS), Zanzibar AIDS Commission (ZAC), National Bureau of Statistics (NBS), Office of the Chief Government Statistician (OCGS), and ICF International 2013. Tanzania HIV/AIDS and Malaria Indicator Survey 2011-12. Dar es Salaam, Tanzania: TACAIDS, ZAC, NBS, OCGS, and ICF International.

APPENDIX I: SCHEDULE OF EVALUATIONS

The schedule of evaluations below applies to all participants on study. Baseline laboratory evaluations are to be conducted within one week before starting of therapy. Scans and x-rays must be done within two weeks prior to the start of therapy. If the participant's condition is deteriorating, laboratory evaluations should be repeated within 24 hours before initiation of the next cycle of therapy.

	Pre-Study	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Treatment Discontinuation	Off Study
Informed consent	X								
Demographics	X								
Medical history	X								
Physical exam	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X			X		X		X	X
Biopsy diagnostic of KS (fixed in formalin)	X[e]								
FACT-G Questionnaire		X[f]			X			X	X
Toxicity evaluations		X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X
Oxygen saturation	X[b]	X	X	X	X	X	X	X	X
Radiologic evaluation	X							X	X
Tumor measurements	X		X		X		X	X	X
Pregnancy test[c]	X[d]		X	X	X	X	X		

a: Total and direct bilirubin, creatinine, SGOT [AST], SGPT [ALT].
b. Within 14 days before enrollment
c. Prior to chemotherapy.
d: Serum pregnancy test (women of childbearing potential).
e. A skin biopsy of an area of KS will be done prior to treatment start if one has not already been done in the past.
f: Prior to initiating treatment.

APPENDIX II: PERFORMANCE STATUS SCALES

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

APPENDIX III: AMC DATA AND SAFETY MONITORING PLAN

(Version 6.0 • March 17, 2017)

Monitoring the Progress of Trials and the Safety of Participants

All AMC protocols that collect safety data follow the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (http://ctep.cancer.gov/guidelines/index.html). All adverse events that meet the NCI's expedited reporting requirements are reported to the Investigational Drug Branch (IDB) of the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application. All expedited adverse event reports are also required to be submitted to the local Institutional Review Board (IRB) of the reporting institution. If NCI holds the IND or no IND is required for a study, the AMC site reports serious adverse events directly to the AMC Operations and Data Management Center (ODMC) via CTEP-AERS; expedited reporting via AdvantageEDC/Advantage eClinical may be permitted for select commercial agent studies per protocol requirements. In some instances, the AMC sites may report serious adverse events directly to a commercial sponsor holding the IND, who will then report the event to the AMC ODMC. Most AMC protocols require sites to report all serious adverse events via CTEP-AERS and the AMC ODMC to forward a copy of the report to the sponsor. The AMC ODMC also distributes all IND safety reports to all investigators upon receipt, and makes these reports available on the password-protected section of the AMC Operations web site. Unless an AMC protocol specifies an alternate plan for the review and submission of serious adverse events, all serious adverse events received by the AMC ODMC will be reviewed by the AMC Medical Monitor at the AMC ODMC. For protocols for which the IDB does not have an assigned drug monitor to review serious adverse event reports, in the event of disagreement between the reporting physician and the AMC Medical Monitor regarding the attribution of the event to the investigational agent(s) (i.e., determination of whether the relationship is unrelated, unlikely, possible, probable, or definite), the AMC Medical Monitor will provide the final determination of the relationship.

The AMC ODMC provides listings of all reported adverse events and serious adverse events to the Protocol Chair and Co-chair(s) for review on a regular basis. The AMC ODMC compiles these events in a tabular format and posts them on the password-protected section of the AMC web site where these reports are updated nightly. The AMC web site is accessible to all AMC investigators, co-investigators, and their staff. Email notification that this information is available on the web site will be sent to all site PIs. It is the responsibility of each site to provide this information to their respective IRBs, if required by their IRB. For blinded studies, the serious adverse events are reviewed and tabulated without treatment assignment. The AMC Medical Monitor will review listings of all reported adverse events on a quarterly basis for safety concerns.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the Protocol Chair and also by the appropriate disease-oriented Working Group during scheduled conference calls. For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the Protocol Chair, AMC Medical Monitor, and Group Statistician determine whether these criteria have been met. For phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the Protocol Chair, AMC Medical Monitor, and

Group Statistician determine whether these criteria have been met.

For phase III trials and other select studies requiring additional oversight, the AMC has formed an independent Data and Safety Monitoring Board (DSMB). Voting members of the DSMB are physicians, a statistician, and a patient advocate. All voting members are from outside the AMC. Nonvoting members are the AMC Group Statistician, the protocol statistician, an AMC Operations Center staff member, two representatives (normally a clinician or statistician) from the Office of HIV AIDS Malignancy (OHAM) or from the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, of the National Cancer Institute (NCI). The DSMB reviews AMC phase III studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all phase III trials are prepared by the AMC Group Statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB Charter. This report addresses specific toxicity concerns as well as concerns about the conduct of the trial. The report may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB Chair to the Group Chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The Group Chair is then responsible for notifying the Protocol Chair and relevant Disease-oriented Working Group Chair before the recommendations of the DSMB are carried out. In the unlikely event that the Protocol Chair does not concur with the DSMB, then the NCI Division Director or designee must be informed of the reason for the disagreement. The Study Chair, relevant Disease-oriented Working Group Chair, Group Chair, DSMB Chair, and NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a formal amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, a summary of the serious adverse events reported to the DSMB is posted to the AMC web site. It is each site's responsibility for conveying this information to its IRB.

Plans for Assuring Compliance with Requirements Regarding the Reporting of Adverse Events (AE)

For trials monitored by the NCI's Clinical Data Update System (CDUS), adverse event information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), adverse event information is transmitted electronically to NCI every two weeks.

The Protocol Chair, AMC Group Chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with the protocol requirements for adverse event reporting. All AMC investigators certify compliance with NCI and FDA requirements for adverse event reporting by signing the AMC Adherence Statement for site membership, the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration and IND studies sponsored by AMC investigators. Investigators are responsible for identifying and reporting all adverse events to the AMC ODMC, CTEP-AERS, and/or sponsors according to

the protocol requirements, and assuring compliance with reporting to the local IRB. Protocol compliance with adverse event reporting requirements is assessed by the AMC ODMC during routine site audits by reviewing the site's source documentation.

The data entry system used for AMC studies, AdvantageEDC/Advantage eClinical (a web-based data entry and enrollment system), is programmed to notify the site investigator, protocol chair, AMC Medical Monitor, and AMC ODMC via email in the event that a site reports an adverse event that meets expedited reporting criteria to NCI and/or FDA. If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC Medical Monitor review reported adverse events on a routine basis to identify adverse events reported by sites that require expedited reporting. The Protocol Chair, AMC Group Chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that termination of the trial or major modification to the protocol is under consideration, the Protocol Chair will convene the AMC Data Coordinator and Disease-oriented Working Group Chair by conference call to discuss the options. For phase I and II trials, the Protocol Chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO) when studies are temporarily or permanently closed. The Cancer Treatment and Evaluation Program (CTEP) of the National Cancer Institute (NCI) must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into AdvantageEDC/Advantage eClinical. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. AMC ODMC staff routinely interacts with site staff to resolve any data problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site Principal Investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option of taking action against the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX IV: FACT-G QUESTIONNAIRE, VERSION 4, ENGLISH AND SWAHILI

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	<u>PHYSICAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy……..	0	1	2	3	4
GP2	I have nausea…….	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family…	0	1	2	3	4
GP4	I have pain……	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill……..	0	1	2	3	4
GP7	I am forced to spend time in bed……...	0	1	2	3	4

	<u>SOCIAL/FAMILY WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends……	0	1	2	3	4
GS2	I get emotional support from my family….	0	1	2	3	4
GS3	I get support from my friends…….	0	1	2	3	4
GS4	My family has accepted my illness……	0	1	2	3	4
GS5	I am satisfied with family communication about my illness…….	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)……	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life……	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad……	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness……	0	1	2	3	4
GE3	I am losing hope in the fight against my illness……..	0	1	2	3	4
GE4	I feel nervous……...	0	1	2	3	4
GE5	I worry about dying…….	0	1	2	3	4
GE6	I worry that my condition will get worse……...	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)….	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life……	0	1	2	3	4
GF4	I have accepted my illness…….	0	1	2	3	4
GF5	I am sleeping well……	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now……...	0	1	2	3	4

FACT-G (Version 4), SWAHILI

Hapa chini kuna orodha ya kauli ambazo watu wengine wenye ugonjwa wako wamesema ni muhimu. **Tafadhali chagua nambari moja katika kila mstari na kuichorea duara ili kuonyesha kadiri kila kauli ilivyokuwa na ukweli kwako wakati wa <u>siku 7 zilizopita.</u>**

	<u>HALI YA KIMWILI</u>	**Hata kidogo**	**Kidogo**	**Wastani**	**Zaidi ya wastani**	**Sana**
GP1	Nina upungufu wa nguvu.....	0	1	2	3	4
GP2	Nina kichefuchefu…….	0	1	2	3	4
GP3	Kutokana na hali yangu ya kimwili nina matatizo ya kukidhi mahitaji ya familia yangu……..	0	1	2	3	4
GP4	Nina maumivu.....	0	1	2	3	4
GP5	Ninasumbuliwa na athari mbaya za matibabu……	0	1	2	3	4
GP6	Ninajisikia mgonjwa.....	0	1	2	3	4
GP7	Ninalazimika kukaa kitandani…..	0	1	2	3	4

	<u>HALI YA JAMII/FAMILIA</u>	**Hata kidogo**	**Kidogo**	**Wastani**	**Zaidi ya wastani**	**Sana**
GS1	Najisikia karibu na marafiki zangu…….	0	1	2	3	4
GS2	Ninapata msaada moyoni kutoka kwa familia yangu…….	0	1	2	3	4
GS3	Ninapata msaada kutoka kwa rafiki zangu……	0	1	2	3	4
GS4	Familia yangu imeukubali ugonjwa wangu.....	0	1	2	3	4
GS5	Nimeridhika na mawasiliano ya familia yangu kuhusu ugonjwa wangu.....	0	1	2	3	4

		Hata kidogo	Kidogo	Wastani	Zaidi ya wastani	Sana
GS6	Ninajisikia karibu na mwenzangu (au mtu anayenisaidia zaidi).....	0	1	2	3	4
Q1	Bila kujali kiwango chako cha sasa katika tendo la kujamiana, tafadhali jibu maswali yafuatayo. Kama hupendelei kujibu maswali haya tafadhali weka alama kwenye kisanduku hiki ☐ na kisha nenda kwenye sehemu inayofuata					
GS7	Nimeridhika na hali yangu ya unyumba……	0	1	2	3	4

Tafadhali chagua nambari moja katika kila mstari na kuichorea duara ili kuonyesha kadiri kila kauli ilivyokuwa na ukweli kwako wakati wa <u>siku 7 zilizopita.</u>

	<u>HALI YA JAZIBA</u>	**Hata kidogo**	**Kidogo**	**Wastani**	**Zaidi ya wastani**	**Sana**
GE1	Nina huzuni…….	0	1	2	3	4
GE2	Nimeridhika na jinsi ninavyokabili ugonjwa wangu……...	0	1	2	3	4
GE3	Nimeanza kukata tamaa kupambana na ugonjwa wangu…..	0	1	2	3	4
GE4	Nina wasiwasi…….	0	1	2	3	4
GE5	Ninahofu kuhusu kifo…….	0	1	2	3	4
GE6	Nina wasiwasi kwamba hali yangu itazidi kuwa mbaya.....	0	1	2	3	4

	HALI YA UTENDAJI	**Hata kidogo**	**Kidogo**	**Wastani**	**Zaidi ya wastani**	**Sana**
GF1	Ninaweza kufanya kazi (pamoja na zile za nyumbani)……	0	1	2	3	4
GF2	Kazi yangu (pamoja na kazi ninayoifanya nyumbani) inaridhisha.....	0	1	2	3	4
GF3	Ninaweza kufurahia maisha.....	0	1	2	3	4
GF4	Nimekubali hali ya ugonjwa wangu.....	0	1	2	3	4
GF5	Ninalala vizuri……	0	1	2	3	4
GF6	Nayafurahia mambo ninayofanya kujifurahisha……...	0	1	2	3	4
GF7	Nimeridhika na hali ya maisha hivi sasa……..	0	1	2	3	4