SUMMARY OF CHANGES

Prospective Observational Study of the Frequency of Site-Specific New and Existing Cases of Cancer in People Living with HIV/AIDS- in Latin America

Version 3.0

NCI Protocol #: AMC-S008
Local Protocol #: AMC-S008

NCI Version Date: 22JAN2021
Protocol Date: 22JAN2021

I. Scientific and Substantive Changes:

#	Section	Comments
1.	What is the purpose?	The number of participants that will take part in this study has been revised from 200 to 400 for consistency with the protocol.

II. Administrative and Editorial Changes:

#	Section	Description of Changes
1.	Global	The version number and date were updated from version 2 dated 02OCT2019 to version 3 dated 22JAN2021.
	What will happen if I decide to partake in this study?	Follow up period was extended and may be completed 1-3 months after enrollment, for consistency with the protocol.

^Notes for Local Investigators:

- The goal of the informed consent process is to provide potential study participants with clear, accurate, unbiased, and sufficient information so that they can make informed choices about participating in research. The ICD is one part of the consent process. It provides a summary of the study, describes foreseeable risks, discusses the individual's rights as a study participant, and documents their willingness to participate. The ICD, however, is only one piece of an ongoing exchange of information between the investigator and study participant.

- Sections that will require edits from local site investigators are highlighted in yellow. These instructions and formatting should remain in the consent form for the local sites. Local sites should remove them from the consent form for patients.

RESEARCH STUDY INFORMED CONSENT DOCUMENT

Study Title for Participants: Counting the number of people living with HIV/AIDS and with new and existing cancers at 4 clinics in Latin America

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: AMC-S008: Prospective Observational Study of the Frequency of Site-Specific New and Existing Cases of Cancer in People Living with HIV/AIDS- in Latin America

OVERVIEW AND KEY INFORMATION

What am I being asked to do?

We are asking you to take part in a research study. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have HIV/AIDS and cancer. We want to understand what types of cancer are treated at this center, and how your cancer has been or will be treated.

Taking part in this study is your choice.

You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

How many people have HIV/AIDS and cancer at four centers in Latin American and what has their care and treatment been?

We are doing this study because we want to find out what the approach for your cancer and to plan future research studies for cancers in people living with HIV/AIDS at these centers in Latin America.

WHAT IS THE USUAL APPROACH?

This study only involves collecting information about you and your cancer treatment. Taking part in this study will not change the way you are given care or treatment for your HIV/AIDS or your cancer.

WHAT ARE MY CHOICES IF I DECIDE NOT TO TAKE PART IN THIS STUDY?

- You may choose to take part in a different research study if one is available.
- You may choose to continue your care without any research.

WHAT WILL HAPPEN IF I DECIDE TO TAKE PART IN THIS STUDY?

If you decide to take part in this study the doctor will collect information about your current HIV

status and treatment, your cancer status and treatment and your current health status at your next visit.

If further treatment for your cancer is planned, in about one to three (1-3) month(s) your doctor will follow-up and collect the same information again. This may happen at another visit, over the phone, or through your medical records.

WHAT ARE THE RISKS AND BENEFITS OF TAKING PART IN THIS STUDY?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this there may be a risk to your privacy. The researchers will make every effort to protect it and your data will be secured.

Benefits

This study will not help you. This study will help the study doctors learn things that will help people in the future.

IF I DECIDE TO TAKE PART IN THIS STUDY, CAN I STOP LATER?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

ARE THERE OTHER REASONS WHY I MIGHT STOP BEING IN THE STUDY?

Yes. The study doctor may take you off the study if:

- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or sponsor (National Cancer Institute).

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to count how many people at your cancer center have HIV/AIDS and cancer and to understand how people are being treated and cared for. We expect to have up to 400 people take part in the trial. This will help researchers understand what new studies may be helpful for your area in the future.

WHAT ARE THE STUDY GROUPS?

There is only one study group in this trial. It will have all people who sign up to the trial in it and

will only be for information collection.

The researchers will count all patients who have HIV and cancer at this site during the study, regardless of whether they agree to take part in the study. This step is for the researchers to understand how many people were asked to join the study, and why some people may not want to take part in the study. The researchers will count patients in a way that cannot be linked to your identity.

WHAT EXAMS, TESTS, AND PROCEDURES ARE INVOLVED IN THIS STUDY?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if you can take part in the study. If you join the study, you will have more questions about your cancer care. Choosing to take part or not in this study will not affect the usual care you will receive.

WHAT RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

General Risks

If you choose to take part in this study, you may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.

WHAT ARE MY RESPONSIBILITIES IN THIS STUDY?

If you choose to take part in this study, you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - if you have been or are currently in another research study.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You will not be charged for taking part in this study.

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study. Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

Taking part in this study may mean that you need to make one more visit to the clinic or hospital than if you were not taking part in the study.

You may:

- Have more travel costs.
- Need to take more time off work.

- Have other additional personal costs.

You will not be paid for taking part in this study.

WHO WILL SEE MY MEDICAL INFORMATION?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor, the National Cancer Institute (NCI) in the United States, and the groups it works with to review research.
- The IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The AIDS Malignancy Consortium (AMC) and its representatives
- Any local regulatory authorities who may have access to the data

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not necessarily be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

WHERE CAN I GET MORE INFORMATION?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required

by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

^Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here. ^

Unknown future studies

If you choose to take part in this study any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

We don't know what research may be done in the future using your health information This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information

How will information about me be kept private?

Your privacy is very important to the study researchers. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

CONTACT FOR FUTURE RESEARCH

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

MY SIGNATURE AGREEING TO TAKE PART IN THE STUDY

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

ATTATCHMENT 1: AMC CERTIFICATE OF CONFIDENTIALITY

The NIH has given the AMC a Certificate of Confidentiality. The Certificate does not mean that the NIH or the U.S. Government recommend that you take part in this study. This Certificate helps us keep your health information private.

Your records for this study will have information that may identify you. This Certificate lets us turn down legal demands for your study records. We can use the Certificate to turn down demands for records from a U.S. court. The Certificate can be used in any federal, state, or local legal matters in the United States. We will use the Certificate to turn down any demands for your study records. The cases where we cannot use the Certificate are explained below.

We cannot use the Certificate to turn down a demand from the U.S. Government for study records. This applies to audits or reviews of the AMC. This also applies to study records that we have to report to the FDA.

The Certificate does not stop you or your family members from sharing your health information. It does not stop you from talking about taking part in this study. You may give written permission for an insurer, employer, or other person to get copies of your study records. If you give permission, we cannot use the Certificate to say no to a request for your study records.

SUMMARY OF CHANGES

Prospective Observational Study of the Frequency of Site-Specific New and Existing Cases of Cancer in People Living with HIV/AIDS- in Latin America

Version 3.0

NCI Protocol #: AMC-S008
Local Protocol #: AMC-S008

NCI Version Date: 22JAN2021
Protocol Date: 22JAN2021

I. Scientific and Substantive Changes:

#	Section	Comments
1.	Synopsis	Due to delays in clinical treatment as a result of COVID-19, timelines of treatment and staging procedures window needs to be increased. Post visit follow up window has been increased to 4 weeks (+6 weeks).
2.	2.2	The anticipated study duration was changed to 21 months (1 year and 9 months) to accurately reflect the timeline for collecting new and existing cancer cases. Due to COVID-19 disruptions to patient referrals, routine clinic visits, and provider illnesses, this study should be extended by one year to capture patient volumes and patient cases presenting to sites as clinic activities begin to resume.
3.	3.3.1	Due to the one-year extension of the study, additional enrollment per site is expected. Thus, the maximum participant enrollment has been changed from 200 participants to 400 participants.
4.	3.3.3	Due to the increase of maximum participants, the Expected Enrollment Demographics table has been updated.

II. Administrative and Editorial Changes:

#	Section	Comments
5.	Global	The version number and date were updated from version 2 dated 02OCT2019 to version 3 dated TBD.
6.	Appendix III	The AMC Data and Safety Monitoring plan was updated from version 6.0 to the current version (9.0). Key revisions include: the addition of an introduction to address the variety of systems the AMC uses for individual trials; changes to the data entry systems used by domestic AMC trials (OPEN/Rave) activated September 1, 2020 and later; participation with a

#	Section	Comments
		single IRB for new domestic AMC protocols; updated procedures for data reporting, determination of requirements for DSMB review, and safety review/pharmacovigilance; and administrative changes (updates to document organization, external links, and group terminology) and to state that the IRB review plan is identified in the protocol, as the AMC is opening international studies subject to review/requirements per their respective regions.

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL S008:

Prospective Observational Study of the Frequency of Site-Specific New and Existing Cases of Cancer in People Living with HIV/AIDS in Latin America

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT04089488
Regulatory Status:	Pursuant to national requirements for each participating site
Protocol Chair:	Matthew Strother, MD (IVR-48877)
Protocol Co-Chair:	Valeria Fink, MD (IVR-621276)

Version 3.0 22JAN2021
NCI Version Date 22JAN2021

AMC PROTOCOL SIGNATURE PAGE

I, _____ , Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol S008 – Prospective Observational Study of the Frequency of Site-Specific New and Existing Cases of Cancer Cases in Persons Living with HIV/AIDS in Latin America (Version 3.0, 22JAN2021),** as written according to the AMC, NCI, applicable national regulatory guidelines, and standards of Good Clinical Practice (GCP, ICH E6). I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

Signature Date (DDMMMYYYY)

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

PROTOCOL ROSTER

AMC Protocol S008

Prospective observational study of the frequency of site-specific new and existing cases of cancer in Persons Living with HIV/AIDS in Latin America

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Fundacion Huesped:
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Contact information is subject to change. For current contact information for clinical sites, please see the protocol roster in the password-protected section of the AMC Operations web site at www.AIDSCancer.org.

PROTOCOL SYNOPSIS

Title:	Prospective observational study of the frequency of site-specific new and existing cases of cancer in People Living with HIV/AIDS in Latin America
Design:	Observational prospective cohort
Accrual Target:	Minimum of 10 cases per participating site; maximum of 400 participants across all centers
Regulatory Status:	Pursuant to national requirements for each participating site
Population:	Participants presenting to HIV treatment programs or cancer treatment programs at collaborating sites, with both HIV and cancer, which may include either a history of malignancy or current diagnosis.
Regimen:	Non-interventional. Data collection will occur via survey procedures and/or medical record review at screening, enrollment, and if available, at 4 weeks following enrollment (+6 weeks).
Anticipated Trial Duration:	1 year, 9 months
Primary Objective:	To determine the frequency of new and existing diagnosed HIV-associated cancers presenting at participating clinical sites in Latin America, based on all presenting cancers (new diagnosis, recurrence, and surveillance cases as defined in Section 3.1.2)
Secondary Objectives:	• Obtain information on the use of diagnostic testing and treatment for the cohort of diagnosed cancers in people living with HIV/AIDS. • To collect current information on participant characteristics for diagnosed cancers in people living with HIV/AIDS (e.g., ART regimen, CD4 count, viral load, etc.)
Exploratory Objectives	• To determine the timelines and requirements for protocol review and approval at the local, regional, and national level. • To familiarize local sites with the online data entry systems used by the AMC.

LIST OF ABBREVIATIONS

ACSR	AIDS and Cancer Specimen Resource
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AMC	AIDS Malignancy Consortium
ANC	Absolute neutrophil count
ART	Antiretroviral therapy
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CDUS	Clinical Data Update System
CIA	Chemiluminescent Immunoassay
CR	Complete response
CRF	Case report form
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	Cancer Therapy Evaluation Program Adverse Event Reporting System
DARF	Drug accountability record form
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EIA	Enzyme Immunoassay
FDA	Food and Drug Administration
FTP	File transfer protocol
HIV	Human immunodeficiency virus
IEC	Institutional ethics committee
IC	Institution and Center
IRB	Institutional review board
IND	Investigational new drug
KPS	Karnofsky performance score
NCI	National Cancer Institute
ODMC	Operations and Data Management Center

PCR	Polymerase chain reaction
PLWHA	People living with HIV/AIDS
PR	Partial response
REB	Research ethics board
RNA	Ribonucleic acid
SAE	Serious adverse event
SOP	Standard Operating Procedure
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objective

To determine the frequency of new and existing diagnosed cancers in PLWHA presenting to participating clinical sites in Latin America, based on all presenting cancers (new diagnosis, recurrence, and surveillance cases as defined in Section 3.1.2).

1.2 Secondary Objectives

1.2.1 Obtain information on the use of diagnostic testing and treatment for the cohort of diagnosed HIV-associated cancer participants.

1.2.2 To collect current information on participant characteristics for diagnosed HIV-associated cancers (e.g., ART regimen, CD4 count, viral load, etc.)

1.3 Exploratory Objectives

1.3.1 To determine the timelines and requirements for protocol review and approval at the local, regional, and national level.

1.3.2 To familiarize local sites with the online data entry systems used by the AMC.

2.0 BACKGROUND

2.1 Study Disease

The AIDS Malignancy Consortium (AMC), as part of its international agenda, is extending its research network into Latin America (LA) and has added 4 sites in the region as of September 1, 2018. Building on lessons learned in the site selection and implementation of clinical trials in Africa, the AMC will utilize a non-interventional, registration-type study to prospectively gather information over a limited time frame on the presentation, evaluation, and treatment of participants newly presenting with HIV-associated cancers (new diagnosis or relapsed/recurrent, excluding dysplasia) that will help to inform the development of future AMC therapeutic trials in LA.

The AMC expansion into LA is supported by the following observations: first, HIV remains common in the region; second, successful HIV treatment programs have resulted in longer survival among people living with HIV/AIDS (PLWHA) and leading to increased cancer incidence; third, regional investment in research and treatment of cancer, and HIV-related malignancy in specific, has been limited. In 2015, there were an estimated 2 million PLWHA in LA, 100,000 new HIV infections, and 50,000 AIDS related deaths[1]. This region has been successful in implementing HIV diagnostic and treatment programs, with an estimated 70% of PLWHA diagnosed, and 44% of eligible adults treated with anti-retroviral therapy (ART)[2]. A recent analysis comparing Latinos in LA versus North America found this population had better continuity of treatment, but conversely had higher mortality, particularly in the first year on ART[3]. Quantifying the impact of cancer on HIV outcomes is hobbled by a dearth of data in this area.

Publications about cancer amongst PLWHA in LA are very limited. The most comprehensive study to date described a cohort of 428 patients with 455 cancers or pre-cancerous lesions amongst the 3372 patients within the Caribbean, Central and South America Network for HIV Research (CCASAnet)[4]. Of the 406 cancers, 82% were AIDS-defining, predominantly Kaposi sarcoma and non-Hodgkin lymphoma, and 18% were Non-AIDS Defining (NADC), predominantly Hodgkin's lymphoma and skin cancers. Approximately half the patients received cancer-specific treatment (chemotherapy, radiotherapy, or combination), with under half of patients reported cured, one-third persistent, and the remainder with unknown outcome. However, improving these outcomes is presently limited by a lack of clinical trials for HIV related cancers in the region.

A Lancet Oncology Commission in 2013 found several hurdles to clinical cancer research in the region, including too few cancer care specialists, limited local expertise in research, and fragmented healthcare systems[5]. A 2015 report by the same body optimistically noted an increased number of oncologists, expansion of cancer registries, and improved national policies and access to care[6]. However, the report still highlighted fragmentation within the healthcare system between urban and rural settings and across the public and private health systems. Further, it was emphasized that there remained inadequate cancer research expertise and infrastructure. This finding in particular highlights the importance of the AMC's proposal to develop research sites in LA, but also highlights the importance of understanding the movement of patients through the health care system to ensure the success of this effort.

The expansion into Sub-Saharan Africa (SSA) emphasized that a structured understanding

of the health delivery services at new collaborating sites is critical to successful partnerships. Building on our prior experience and lessons learned from SSA, allowing targeted strategic investment in education and infrastructure, we propose a non-interventional registration study that will provide practical information about HIV and cancer care, research infrastructure, and the management of HIV+ cancer patients, while also introducing the new AMC sites to the group's online data entry system.

2.2 Study Design and Rationale

This protocol will develop a prospective cohort of newly diagnosed and previously diagnosed cancers in each site's HIV patient populations.

Following local/regional/national regulatory approval of this protocol, sites will be asked to prospectively capture cancer diagnoses in the setting of HIV infection, that present to the sites. The convenience sampling used in this protocol will only capture participants presenting at participating centers and will not actively identify participants in historical records. Data collection will occur over a period of 1 year, and 9 months. All participants presenting to sites with a diagnosis of HIV-associated cancer will be asked to participate. All patients presenting to the clinic with HIV and a diagnosis of malignancy will be recorded on a screening list. In participants who consent to participate in the data collection, data captured will include, but not be limited to, the following:

Table 2-A: Model Participant Data Set

Demographics	Age, sex, etc.
HIV Care	Whether current HIV care is being received at the enrolling institution, current ART regimen, date of diagnosis, method of diagnosis, current OIs, current medications, recent viral load, CD4 count
Status of Diagnosis	New Diagnosis, pre-treatment phase, and treatment phase Prior Diagnosis, in remission (within 5 years of initial diagnosis) Prior Diagnosis, recurrent, pre-treatment, treatment phase, or no treatment planned
Cancer Diagnosis	Cancer diagnosis, date cancer diagnosed, diagnostic methods (cytology, histology), pathology performed, date of pathology, staging, staging methods (clinical, radiographic, surgical), date(s) of staging (new and recurrent cancer only), current ECOG PS, current laboratory values
Cancer Treatment Plan	Detailed prior/planned treatment (e.g., chemotherapy, radiation, surgery, or best supportive care/watchful waiting). Whether current cancer care is being received or will occur at the enrolling institution. Timeline of planned treatment (i.e., start date).

For participants initiating therapy (new or recurrent) or currently under treatment, a short interval follow-up (approximately 1-3 months), will be used to ascertain the current vital status, and current state of planned cancer therapy. The data collected at this later time point will be limited, as the intent of this data capture is to ascertain the relationship between planned therapy and therapy received. These data will include any cancer-specific therapy initiated since registration, the start date of that therapy, and whether the therapy has had significant delays to initiation or interruptions of therapy.

Please see Section 7.2 for specific data to be collected during this protocol.

3.0 PARTICIPANT SELECTION

A rostered AMC investigator (CTEP-registered physician investigator or Non-Physician Investigator) or delegated clinical staff (CTEP-registered Associate Plus) must document that each protocol participant meets all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied 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: S008 - ___ ___ ___ - ___ ___ ___ ___ ___

Participant's Initials (L, F, M *[optional]*): ___ ___ ___

NOTE: All questions regarding eligibility should be directed to the study chair.

3.1 Eligibility Criteria

____ 3.1.1 HIV positive. Documentation of HIV-1 infection by means of any one of the following:

- Documentation of receipt of ART by a licensed health care provider (Documentation may be a record of an ART prescription in the participant's medical record, a written prescription in the name of the participant for ART, or pill bottles for ART with a label showing the participant's name);
- HIV-1 RNA detection by a licensed HIV-1 RNA assay demonstrating >1000 RNA copies/mL, and supported by a licensed screening antibody and/or HIV antibody/antigen combination assay;
- Any licensed HIV screening antibody and/or HIV antibody/antigen combination assay confirmed by a second licensed HIV assay, such as a HIV-1 Western blot confirmation or HIV rapid multispot antibody differentiation assay.

Note: The term "licensed" refers to a kit that has been certified or licensed by an oversight body within the participating country and validated internally.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) 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 RNA viral load.

____ 3.1.2 Must have a current or prior (within the last 5 years) diagnosis of cancer – but there is no restriction of the number or type of prior treatments. Participants will qualify under one of three categories:

- New diagnosis – no prior treatment for current malignancy. May be prior to, or currently receiving the first line of therapy.
- Prior diagnosis (within 5 years), in remission – Not currently on cancer treatment other than cART. Prior treatment for malignancy can include surgery, radiation, or chemotherapy (or cART initiation in KS). No restriction on number of prior lines of therapy.
- Prior diagnosis, recurrent – Considering or currently receiving treatment that is not first line. No restriction on the number of prior lines of therapy

____ 3.1.3 Age > 18 years. Date of birth and age should be determined based on best possible information or documentation available.

____ 3.1.4 Ability to understand and the willingness to provide informed consent document.

3.2 Exclusion Criteria

Participants not meeting all criteria above in Section 3.1 are ineligible.

3.3 Number of Participants to be Enrolled

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the participants or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

3.3.1 Proposed sample size

This study will enroll a minimum of 10 participants per site. If fewer than 10 participants are identified at a site, the AMC will work with site on improvement of potential participant identification. A maximum of 400 participants will be accepted for this registration study. Accrual will be completed once the target trial duration has elapsed.

3.3.2 Accrual rate

Approximately 2 participants per month per site.

3.3.3 Expected Enrollment Demographics

INTERNATIONAL PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
Indigenous	0	0	14	26	40
Asian	0	0	0	4	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African	0	0	6	10	16
White	0	0	50	110	160
More Than One Race	0	0	60	120	180
Total	0	0	130	270	400

3.4 Participant Enrollment Procedures

Sites must have this protocol approved by their Institutional Review Boards (IRB) and be registered for study participation with the AMC Operations and Data Management Center (ODMC) before they may enroll participants.

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 Advantage eClinical[SM] Internet Data Entry System (Advantage eClinical). Enrollment and data collection will occur via the AMC Internet Data Entry System.

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 must be enrolled on-line via Advantage eClinical within 1 week of consent. 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 001-301-251-1161) for further instructions.

4.0 TREATMENT PLAN

This is a descriptive study. No intervention will be administered as part of this protocol. Please refer to the clinical and laboratory evaluations and statistical sections for a description of the trial procedures.

5.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

As this study is non-interventional and focuses on data collection for cancer diagnosis and treatment initiation with limited follow-up, no adverse event data will be collected.

6.0 PHARMACEUTICAL INFORMATION

Not applicable (non-interventional study).

7.0 CLINICAL AND LABORATORY EVALUATIONS

Evaluations required for this protocol are enumerated below and summarized in the Schedule of Events in Appendix I.

7.1 Screening

All presenting HIV+ participants with a histologically confirmed diagnosis of cancer (prior, within 5 years, or current) will be tracked on a screening list and approached to participate in AMC-S008.

To determine the types of cancer cases that present to the clinical sites, it is requested that all participants presenting at these sites have a minimum set of data collected. As this will be performed prior to formal consent, this data collection will be done in a de-identified fashion. Data collected on participants presenting to the clinical site will include the participant's age, sex at birth, and type of cancer. This information will be maintained separately from data on enrolled cases and will not be recorded with any codes or data elements that could be linked to the participant's identity. This data will be compared to the total number of enrolled participants at each site to estimate the proportion of participants who consent to participate in this trial.

7.2 Enrollment Data Collection

Following informed consent, additional, identifiable data will be collected, as outlined below.

7.2.1 Age, date of birth, sex at birth

7.2.2 Whether current HIV care is being received at the enrolling institution, current ART regimen, data of HIV diagnosis, method of HIV diagnosis, current opportunistic infections, current medications.

7.2.3 Current ECOG performance status (see Appendix II)

7.2.4 Estimated life expectancy

7.2.5 Status of cancer diagnosis (one of the following)

- New diagnosis, pre-treatment phase
- New diagnosis, treatment phase
- Prior diagnosis, in remission (within 5 years of initial diagnosis)
- Prior diagnosis, recurrent, pre-treatment phase
- Prior diagnosis, recurrent, treatment phase
- Prior diagnosis, recurrent, no treatment planned

7.2.6 For participants with a new diagnosis (pre-treatment or treatment), the following will be collected:

7.2.6.1 Cancer diagnosis, date of diagnosis, method of diagnosis (cytology, histology), type of pathology performed (H&E, immunohistochemistry, other), data of pathology, staging, staging methods (clinical, radiographic, surgical), date(s) of staging, most recent laboratory values (this would

include complete blood count, renal and liver function, electrolytes, CD4 count, and HIV viral load).

7.2.6.1 Detailed planned or current treatment. This should encompass surgical interventions, radiotherapy, and chemotherapy (agent names), including dates of planned or current therapy, and whether cancer care is being received or will occur at the enrolling institution.

7.2.7 For participants with a prior diagnosis in remission, the following will be collected:

- Cancer diagnosis, date of diagnosis
- Current method of post-treatment surveillance (clinical, laboratory, radiographic), and current schedule of follow-up with this center, current laboratory values (this would include complete blood count, renal and liver function, electrolytes, CD4 count, and HIV viral load).
- Prior method of diagnosis (cytology, histology), pathology performed, date of pathology, staging, staging methods (clinical, radiographic, surgical). Records from a prior diagnosis/treatment should be requested, but if they are unavailable, participant report will be sufficient.
- Prior treatment. This should encompass surgical interventions, radiotherapy, and chemotherapy. Records from a prior diagnosis/treatment should be requested, but if they are unavailable, participant report will be sufficient.

7.2.8 For participants with a prior diagnosis, recurrent (pre-treatment, treatment, or no planned treatment) the following will be collected:

- Initial cancer diagnosis, date of diagnosis
- Prior method of diagnosis (cytology, histology), pathology performed, date of pathology, staging, staging methods (clinical, radiographic, surgical), date(s) of staging. Records from a prior diagnosis/treatment should be requested, but if they are unavailable, participant report will be sufficient.
- Prior treatment. This should encompass surgical interventions, radiotherapy, and chemotherapy. Records from a prior diagnosis/treatment should be requested, but if they are unavailable, participant report will be sufficient.
- Current date of cancer diagnosis, method of diagnosis (clinical, cytology, histology), pathology performed, date of pathology, staging, staging methods (clinical, radiographic, surgical), date(s) of staging, current ECOG Performance Status (PS), current laboratory values (this would include complete blood count, renal and liver function, electrolytes, CD4 count, and HIV viral load).
- IF THERAPY IS PLANNED OR UNDERWAY: Detailed planned or current treatment. This should encompass surgical interventions, radiotherapy, and chemotherapy, dates of planned or current therapy, and whether cancer care is being received or will occur at the enrolling institution.
- IF NO THERAPY IS PLANNED: Reason for no further therapy, e.g., if the decision for no therapy is based on lack of options for treatment, lack of benefit

of further treatment, or participant choice not to pursue further treatment.

7.3 Follow-up Evaluations

For any participants enrolled in AMC-S008, with either planned or current therapy, for both new diagnosis and prior diagnosis, recurrent, a short interval follow-up will be conducted at 4 weeks (+ 6 weeks). Participants can be contacted in person during a planned return visit within this window or can be contacted by telephone if no further clinical appointments occur within this window. If the participant cannot be reached and the information is available in an electronic medical file, this follow up can occur passively via review of medical records.

7.3.1 Is the participant still in follow-up? Last date participant seen in clinic. Current vital status, current ECOG PS.

7.3.2 Current status of treatment plan: planned, no longer planned, ongoing, completed.

7.3.3 For participants in whom treatment is still planned.

- Has the planned therapy changed since enrollment?
- Is the planned start date the same as prior?
- If the planned start date has changed, the reason.

7.3.4 For participants in whom treatment is no longer planned.

- Why the treatment is no longer planned?

7.3.5 For participants in whom treatment is in process.

- Is the current therapy different than the prior planned treatment?
- Start date of current therapy?
- If start date changed, the reason.
- Have there been any delays in treatment thus far, and if so, why?

7.3.6 For participants who have completed therapy.

- Date therapy completed.
- Was therapy completed because planned treatment had been achieved, treatment determined to not be of benefit, change to new therapy based on toxicity or progression, or another factor?

8.0 MEASUREMENT OF EFFECT

This is a non-interventional protocol. All data reported on the effect of prior treatment for malignancy will be reported based on existing medical records or the local standard of care.

The following definitions will be employed for case classification and data reporting.

First-line therapy	All therapy performed as part of a treatment plan with a new diagnosis of cancer, including surgery, radiotherapy, and chemotherapy, alone or in combination.
Therapeutic encounter	The period between initiation of a planned therapy and completion of that episode of planned therapy. If the planned therapy changes due to changing clinical circumstances, this is now a new therapeutic encounter (e.g., with progression on first-line therapy R-CHOP, the next treatment is a new therapeutic encounter).
Site-specific frequency of new cases	Total number of participants that present to the site with a first diagnosis of cancer. This encompasses the period from histologically proven cancer to completion of planned first-line therapy or discharge with no anti-cancer treatment planned.
Site-specific frequency of new and existing cases	Total number of participants that present to the site with a diagnosis of cancer within the last 5 years. This includes participants in treatment, surveillance, or best supportive care.
New diagnosis	Status that includes the period from histologically proven cancer to completion of all planned first-line therapy. A second malignancy will be captured as a new diagnosis. Examples include a transformed lymphoma in the setting of the low-grade lymphoma or development of vulvar cancer in the setting of a history of treated cervical cancer.
Prior diagnosis, in remission	Status that includes the period from completion of first-line therapy until evidence of disease progression. This could encompass participants with no evidence of disease or stable disease that is not progressing.
Prior diagnosis, recurrent	Status that includes the period following evidence of progression of the previously diagnosed cancer in a participant who has completed a prior therapy. This does not encompass new second malignancies.
Pre-treatment phase	The period in which a participant has a histologically diagnosed cancer, with cancer-specific treatment planned but not yet initiated.
Treatment phase	The period in which the participant has started therapy for cancer. This can include surgery, radiation, and/or chemotherapy. This period completes when all planned therapy has been completed within a therapeutic encounter.
No treatment planned	The point at which no further active cancer treatments are

	planned. Initiation of best supportive care or palliative care.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints and Analytic Plan

This study will utilize a prospective cohort design to identify the frequency of new and existing cancer cases among PLWHA receiving care at the site.

The primary endpoint will be the estimates of site-specific frequency of new and existing cases presenting with HIV and cancer presenting over 1 year, 9 months at the clinical sites.

For each geographic site and type of cancer, the number of new and existing cancer cases will be estimated using a 95% Poisson confidence interval.

Secondary endpoints will include:

- Information on the use of diagnostic testing and treatment for cancers diagnosed in HIV-positive individuals. The frequency of diagnostic testing modalities and cancer treatment regimens will be summarized for cancer.
- Current information on the HIV treatment and disease characteristics (e.g., ART regimen, CD4 count, viral load, etc.) of HIV-positive individuals diagnosed with cancer. For each cancer, summary statistics will be used to describe the HIV treatment regimens and disease characteristics.

Exploratory endpoints will include:

- Timelines and requirements for protocol review and approval at the local, regional, and national level.
- The familiarization of local sites with the online data entry systems used by the AMC.

9.2 Sample Size/Accrual Rate

2 participants per month, per site.

This study will enroll a minimum of 10 participants per site. If fewer than 10 participants are identified at a site, the AMC will work with site on improvement of potential participant identification. A maximum of 400 participants will be accepted for this registration study.

10.0 ROLE OF DATA MANAGEMENT

10.1 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.

10.2 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.

10.3 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.

11.0 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 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/institutional ethics committee (IEC) 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, which specifically approves the protocol and informed consent, before participant enrollment. The IRB 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 all participants who will be enrolled for data collection per section 7.2. 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 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.

The activities described in Section 7.1 for tracking screened cases preceding trial entry list qualify as exempt human subjects research under 45 CFR 46.101(b)(4) as the data collected will be limited to the age, sex at birth, and cancer diagnosis for patients who present to the clinic with diagnoses of cancer and HIV infection. The data will be recorded in a manner that is not linked to any other information in the patient's medical records or enrollment in the trial. This data will be used solely to estimate the number and types of cancer cases that present to the site, and to estimate the proportion of cases who consent for enrollment for data collection, as compared to the total number of enrolled cases.

11.1.1 Local, regional, and/or national regulatory review

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local, regional, and national laws and regulations governing the conduct of clinical trials involving human subjects, and the confidentiality and disclosure of health information. Each participating center will be responsible for ensuring compliance with applicable law for its respective locality. Documentation regarding the approval of the competent authority or exemption from further review will be required for protocol activation.

In the event that the local IRB or competent authority for the region requires a waiver of informed consent for the activities described in Section 7.1 for tracking screening cases preceding trial entry, the site will be required to obtain this approval before the site may initiate protocol data collection.

11.2 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 the national regulatory body (if applicable) must be sent to the ODMC.

12.0REFERENCES

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2. Perez, F., Gomez, B., Ravasi, G. & Ghidinelli, M. Progress and challenges in implementing HIV care and treatment policies in Latin America following the treatment 2.0 initiative. *BMC Public Health* 15, (2015).
3. Cesar, C. *et al.* Health outcomes among HIV-positive Latinos initiating antiretroviral therapy in North America versus Central and South America. *J. Int. AIDS Soc.* 19, 20684 (2016).
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5. Goss, P. E. *et al.* Planning cancer control in Latin America and the Caribbean. *Lancet Oncol.* 14, 391–436 (2013).
6. Strasser-Weippl, K. *et al.* Progress and remaining challenges for cancer control in Latin America and the Caribbean. *Lancet Oncol.* 16, 1405–1438 (2015).

APPENDIX I: SCHEDULE OF EVALUATIONS

The schedule of evaluations below applies to all participants on study.

	Pre-Study	Enrollment	Week 4 (+ 6 weeks)*
Informed consent	X		
Demographics	X		
HIV history		X[1]	
Cancer history		X[1]	X[2]
Performance status		X	X
Laboratory data collection		X[1]	X[2]
* Subjects in whom no further treatment is planned after enrollment do not require the week 4 follow-up [1]Please see Section 7.2 for specific records to be collected. [2]Please see Section 7.3 for specific records to be collected.			

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 9.0 • October 6, 2020)

Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct (which may include trials conducted in the U.S., international sites, or both), IND sponsor (AMC investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

Monitoring the Progress of Trials and the Safety of Participants

Routine and expedited AE reporting

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a clinical investigator for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S., all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND sponsor or its designee will issue the determination as to whether the AE requires IND safety reporting to FDA as a serious and unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND,

in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the sponsor or sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC investigators or industry sponsors.

Expedited reporting to the Institutional Review Board (IRB)

The requirements for IRB review will be identified in the protocol section on ethical and regulatory obligations. All AMC trials initiated before September 1, 2020 and all international sites for all AMC studies are subject to local IRB review; only U.S. sites are subject to the NCI requirement to use a single IRB for protocols initiated on or after September 1, 2020. For trials subject to local IRB review, the site principal investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the single IRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to that RB, in accordance with its standards of procedure.

To comply with investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all investigators upon receipt from the sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (U.S. trials subject to single IRB review/CTEP IND agents). The site clinical investigator responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

Procedures for monitoring trial progress and pharmacovigilance

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC investigators and their staff It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

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 Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under investigation. Findings from these reviews are communicated to the protocol chairs and all AMC investigators, and posted to the AMC Operations web site.

Data and Safety Monitoring Board Review (DSMB) review

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved by CTEP and, as applicable, required by the IRB of record.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review 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 issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC 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 or designee is then responsible for notifying the protocol chair and relevant SWG 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 OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG 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 protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC investigators and staff. It is each site principal investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by a single IRB, the AMC ODMC will support notification to the IRB as required per its procedures.

Cohort trial reviews not subject to DSMB review

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 protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable 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 protocol statistician determine whether these criteria have been met.

Plans for Assuring Compliance with Requirements Regarding AE Reporting

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration, and also for AMC IND studies sponsored by AMC investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that meets expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). 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 AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials

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

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 temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC investigators, the AMC DSMB will be notified of the suspension and the reason. 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), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP 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 the applicable clinical data entry system for the trial. 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. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission 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 to implement remedial action(s) for 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.