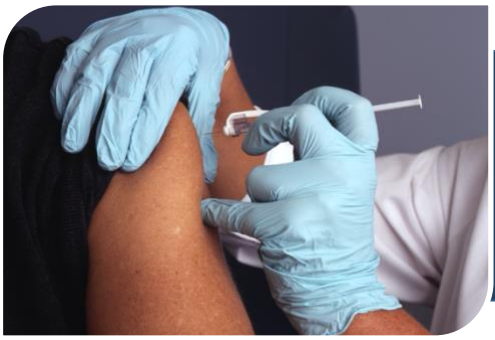
NATIONAL CANCER INSTITUTE
Division of Cancer Prevention

ULACNet: US-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network



Optimizing dosing and delivery and evaluating new indications for HPV prophylactic vaccines

Evaluating new biomarkers and technologies for improving accuracy of cervical and anogenital cancer screening and triage

Evaluating novel non-excisional treatment approaches for HPV-related precancers

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National Cancer Institute
US-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network (ULACNet)

Program Guidelines

December 2020

Division of Cancer Prevention

National Cancer Institute

National Institutes of Health

Table of Contents

I. Introduction

a. Purpose of Program Guidelines

The United States-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network (ULACNet), funded and supported by the National Cancer Institute (NCI), Division of Cancer Prevention (DCP), focuses on developing evidence to improve and optimize approaches for prevention of HPV-related cancers in people living with HIV in low- and middle-income countries (LMICs) in the Latin American and Caribbean (LAC) region via a U54 Partnership Centers Cooperative Agreement mechanism. This document provides guidelines and instructions for operationalizing ULACNet protocols for grantees and NCI/DCP staff. These guidelines are intended to be used as a resource for the ULACNet to efficiently facilitate the design, conduct, and completion of clinical trials for improving prevention of HPV-related cancers in people living with HIV. These guidelines supplement instructions from the Funding Opportunity Announcement (FOA) RFA-CA-18-018.

b. ULACNet Background, Purpose, and Objectives

i. Background

The human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic continues to pose a major global disease burden, with over 30 million individuals infected worldwide, of whom more than 90% reside in LMICs. Those individuals are increasingly accessing affordable combination antiretroviral therapy for HIV infection. Patients receiving antiretroviral therapy are living longer but are at increased risks for cancers etiologically linked to human papillomavirus (HPV), including cervical, vulvar, vaginal, anal, and oropharyngeal cancers. These HPV-related cancers remain a leading cause of mortality and morbidity among people living with HIV in LMICs. The availability, over the past decade, of highly effective prophylactic HPV vaccines offers an unprecedented opportunity for primary prevention for these cancers. Furthermore, screening for and treating women with precancerous lesions is a highly effective strategy for secondary prevention of cervical cancer. Approaches for screening for other HPV-related cancers (e.g., anal cancer) are still under active clinical investigation. Protocols for prevention of HPV-related cancers in people living with HIV have not been refined, particularly in the context of resource-constrained settings where traditional prevention-oriented services (e.g., periodic cervical cancer screening, or HPV vaccination) are either lacking or are sub-optimally functioning. Whereas several efforts have been undertaken to quantify the burden of HPV-associated neoplastic disease in populations of people living with HIV, there have been very few efforts to generate evidence on the utility of clinical strategies to prevent such cancers. In fact, the mere availability of prevention tools or approaches (e.g., HPV vaccines, novel screening tests, non-surgical treatment strategies) does not automatically translate to guidelines for their utilization among people living with HIV. Collaborative clinical trials that seek to answer outstanding research questions related to optimizing frequency and algorithms for implementation of existing and novel interventions are needed to guide evidence-based prevention and treatment strategies for persons living with HIV/AIDS.

The LAC region has a high dual clinical burden of HIV/AIDS and HPV-related cancers. It is estimated that 2 million people are living with HIV in the LAC region, and about 100,000 are newly infected annually. Annual new HIV infections among adults increased by 2% in Latin America and by 9% in the Caribbean between 2010 and 2015. Nine countries in the region have generalized HIV epidemics, and most others have concentrated epidemics among their 'most-at-risk' population subgroups including female sex workers and their clients, men who have sex with men and other gender/sexual minorities, and injection drug users. The LAC region also has some of the highest incidence and mortality rates from cervical cancer in the world. The age-adjusted cervical cancer incidence rates range from 20 to 80 per 100,000 women per year, which is 3- to 11-times higher than in the United States. Governments in LAC region are demonstrating

stronger commitments than ever before to address burdens of both HIV/AIDS and cervical and other HPV-related cancers. Several LAC countries have led the way in creating models of HIV care for other LMICs by providing universal access to affordable antiretroviral drugs for people living with HIV, along with faciliatory health care access policies towards at-risk groups, and enhanced linkages for implementation with non-governmental organizations. Recent strong commitments from LAC region governments have attempted to increase utilization of multilateral bulk procurement mechanisms such as the Pan American Health Organization (PAHO) Revolving Fund to improve cervical cancer screening and prevention, as well as incorporation of HPV vaccination as part of national immunization programs. There are strong and well-established academic global health partnerships between US academic medical centers and LAC region country counterparts that have hosted long-established NIH-funded clinical trials infrastructures. Such settings in the LAC region that provide a highly capable clinical research workforce and infrastructure for conducting high-quality cancer prevention clinical trials within high clinical disease burden settings also provide the opportunity to demonstrate and evaluate strategies for eventual translation to other LMIC settings.

This network of highly experienced, international researchers and sites will design, conduct, and oversee high-impact, policy-translatable clinical trials via effective collaborative ULACNet Partnership Centers.

ii. Purpose

The purpose of the ULACNet is to efficiently facilitate the design, conduct, and completion of clinical trials for improving prevention of HPV-related cancers in people living with HIV.

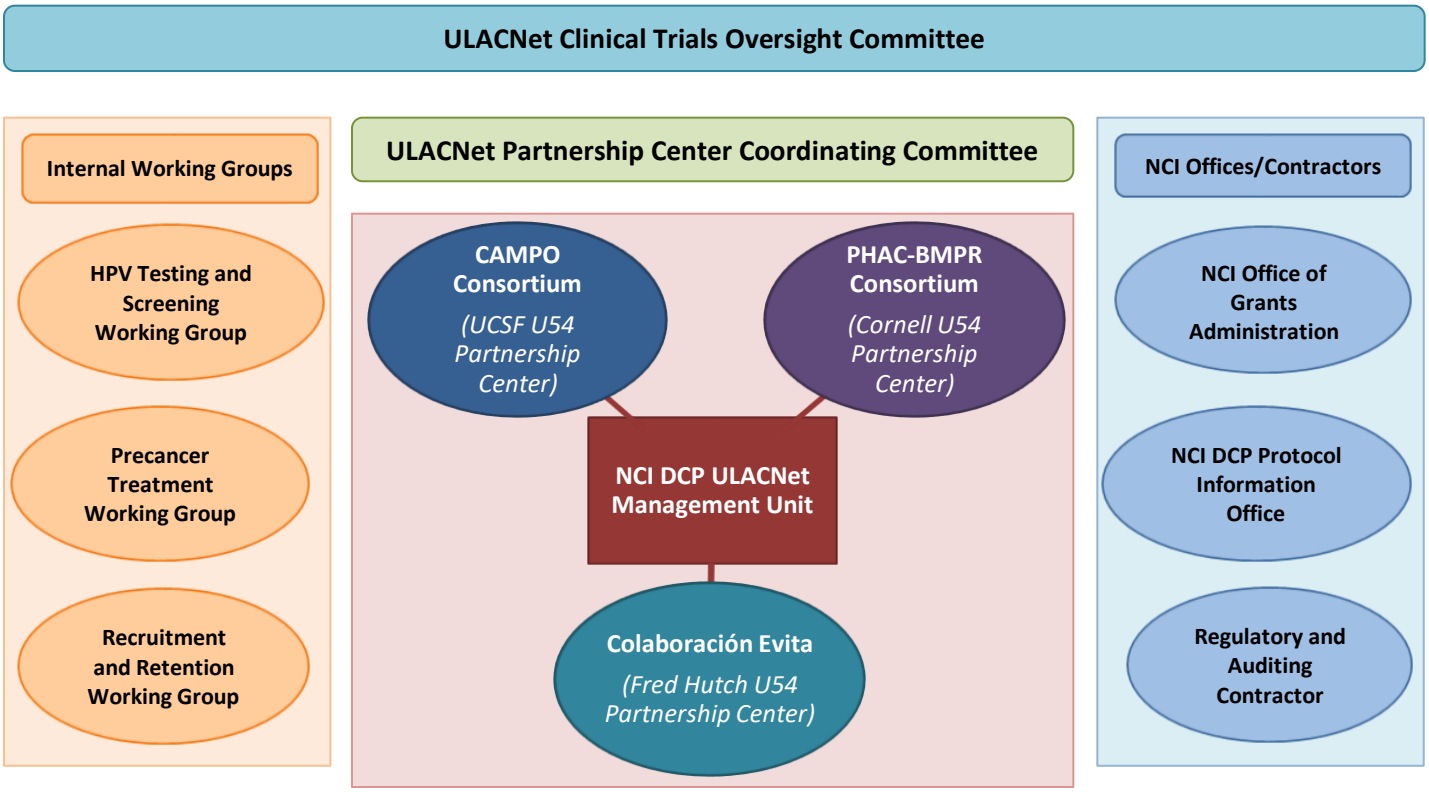
iii. Objectives

The ULACNet Partnership Centers will:

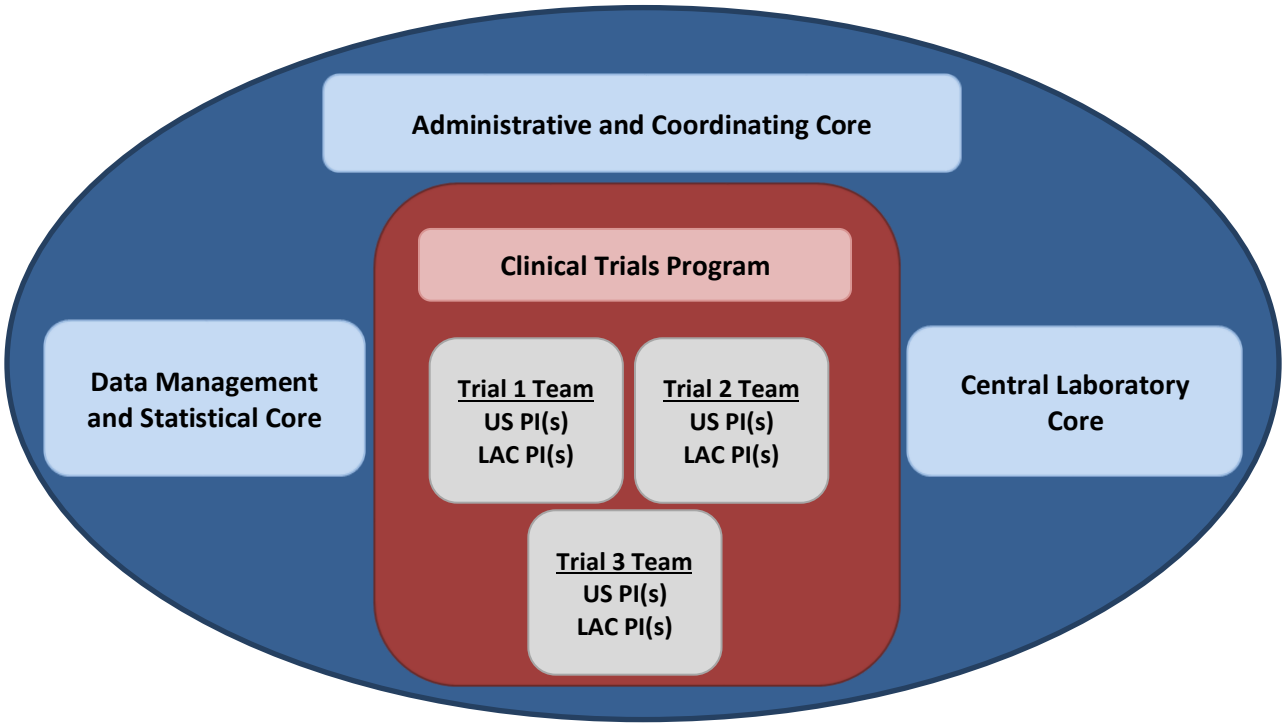
- propose, develop, and conduct highly meritorious clinical trials focused on prevention of HPV-related cancers in people living with HIV. These clinical trials will be conducted jointly by the U.S. institution and LAC region country institution at clinical sites in the partnering LAC region countries.
- enhance the ability of the partnering LAC region institution(s) to serve as a national and regional resource for clinical research in prevention of HPV-related cancers in people living with HIV.

II. Organizational Structure for ULACNet

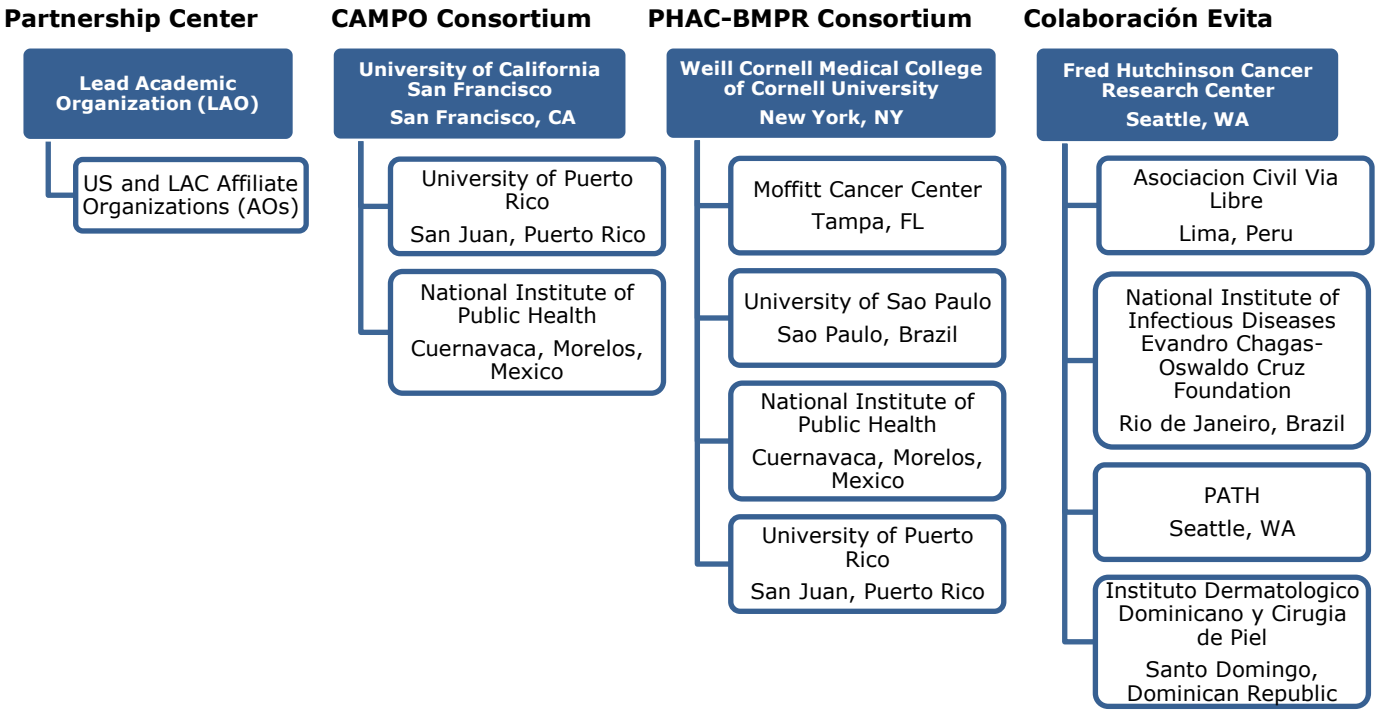
a. Network Stucture



b. Structure of Each ULACNet U54 Partnership Center



c. Network Collaborators



d. ULACNet Partnership Centers

Each Partnership Center is a collaboration between a research institution in the United States as the Lead Academic Organization (LAO) and Affiliate Organizations (AOs) in the US and low- and middle-income countries (LMICs) in the Latin American and Caribbean (LAC) region.

Each Partnership Center consists of the following components:

i. Administrative and Coordinating Core
ii. Data Management and Statistical Core
iii. Central Laboratory Core
iv. Clinical Trials Program

i. Administrative and Coordinating Core

Each Administrative and Coordinating Core is responsible for their Partnership Center's overall project administration, coordination, communication, and management including:

- Training and study monitoring
- Providing regulatory support in conjunction with the DCP Regulatory Contractor
- Liaising with NCI Staff
- Recruitment, retention and adherence efforts
- Convening and liaison with data safety and monitoring boards
- Facilitating career development opportunities for young investigators and trainees
- Ensuring scientific integrity, research productivity, and regulatory and fiscal responsibilities
- Ensuring that all press releases reference the grant number and the program name: *US-Latin American-Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network (ULACNet)*

ii. Data Management and Statistical Core

Each Data Management and Statistics Core will provide for their site technical assistance for

statistical considerations in protocol design, and assist with data management, data analysis, and results reporting, and scientific publications. Duties include:

- Providing data management and reporting support to the Partnership Center
- Creating and enforcing data management policies, formulating management techniques for quality data collection to ensure adequacy, integrity, and legitimacy of data, and devising and implementing secure procedures for data management and analysis with attention to all technical and regulatory aspects
- Providing data management support for tracking and improving participant accrual
- Supporting routine and ad-hoc reporting of mandatory clinical trials data to NCI
- Supporting monitoring and auditing of clinical trials data and processes at participating clinical sites to ensure that all relevant good clinical practice (GCP) guidelines, protocol requirements, applicable in-country and US federal regulatory requirements/regulations, and NIH/NCI/DCP policies are followed
- Providing support for the development, presentation, and dissemination of educational materials and other capacity building resources for recruitment and retention activities
- Supporting efforts in management and storage of biospecimens from ULACNet trials and working with the appropriate NCI/DCP designated biospecimen repository

iii. Central Laboratory Core

Each Central Laboratory Core will be responsible for supporting the laboratory investigations in each clinical trial planned by the Partnership Center, as well as conducting central pathology endpoint reviews, quality assurance for virologic/immunologic testing, and liaise with external labs for specialized biomarker assays for their site. Specific responsibilities include:

- Supporting the performance of laboratory assays for the primary aims of the clinical trials as well as any secondary/exploratory aims and correlative science studies
- Planning and undertaking rigorous quality management protocols to ensure internal and external validity of laboratory data
- Developing standard-operating protocols (SOPs) for each protocol on handling study biospecimens
- Optimizing the processes of sample collection, handling, shipment/transfer, and short- and long-term storage and retrieval
- Ensuring domestic and international shipments are in compliance with International Air Travel Association (IATA)-regulations
- Supporting training and career development of early career investigators in lab research

iv. Clinical Trials Program

The main scientific component of each Partnership Center is centered on designing and conducting three clinical trials focused on prevention of HPV-related cancers in people living with HIV in clinical research sites based in LAC region partnering institutions. The emphasis and choice of focus areas and trials should be reflective of the LAC countries' priorities, capabilities of each clinical research site’s infrastructures and the available pool of potential research participants for enrollment and retention, and access to appropriate prevention intervention technologies and agents.

Each trial will focus on one or more of the following three broad prevention science areas (Fig 1):

- Area 1: HPV immunoprevention in people living with HIV
- Area 2: Cervical cancer screening and triage approaches for women living with HIV
- Area 3: Evaluating non-surgical strategies for treating HPV-related precancerous lesions among people living with HIV

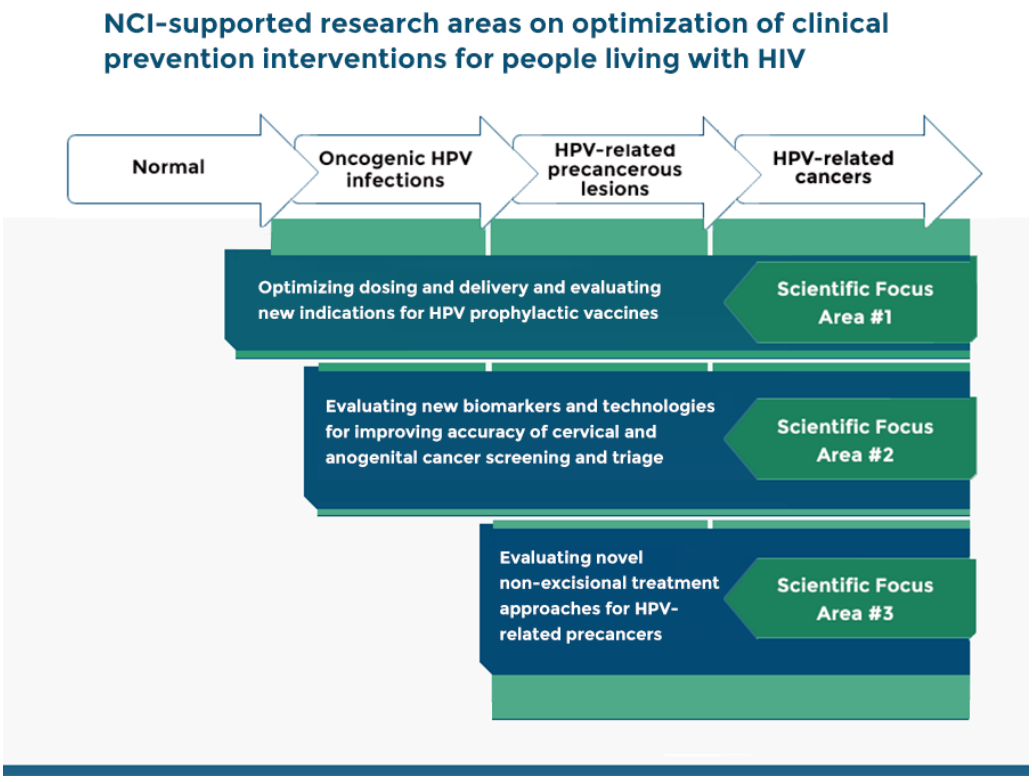
The trials are expected to address issues that are both high-priority to the partnering LAC countries and are considered aligned with HIV/AIDS research priority areas for the NIH (NOT-OD-20-018). The highest overarching priorities for HIV/AIDS research and guidelines for determining the use of HIV/AIDS-designated funds effective FY 2021 to FY 2025 are: 1) reduce the incidence of HIV/AIDS, including the development of safe and effective HIV/AIDS vaccines and microbicides; 2) develop the next generation of HIV therapies with improved safety and ease of use; 3) discover a cure for HIV/AIDS; and 4) reduce HIV-associated comorbidities and coinfections. Basic research, health disparities, behavioral and social sciences research, epidemiology, information dissemination, implementation sciences, and training that cut across the four priority areas are also supported.

Each trial will:

- be supported by compelling underlying biological rationale and preclinical data
- efficiently and effectively enroll clinical trial participants
- be conducted with available resources and completed within proposed accrual timelines
- be well integrated with the general current state of the field and relevance of clinical and public health needs in the LAC region communities in which it is being implemented

Prior to protocol approvals and study launch, the ULACNet Partnership Center must finalize preparatory steps for the clinical trials (e.g., enrollment strategies, refinement of data collection instruments, staff training, etc.). Each clinical trial protocol must have appropriate IRB approval(s) on file and be reviewed and approved by the Clinical Trials Oversight Committee before activation through the Partnership Center.

Figure 1. NCI-supported research areas on optimization of clinical prevention interventions for people living with HIV



III. Program Governance

a. ULACNet Coordinating Committee

This committee, with representation from the Partnership Centers PD/PI and NCI staff, will be responsible for coordinating and harmonizing scientific activities across the funded ULACNet Partnership Centers.

Committee Chair - The Coordinating Committee will be chaired on a rotating basis once per year by each of the three Partnership Center PDs/PIs.

Committee Members

- Each PC may invite multiple members to serve on this committee, but each PC will have one collective vote to be cast by the contact PI.
- NCI DCP ULACNet Management Unit staff will participate on the Committee, and the ULACNet Director (serving as NCI Overall Program Scientist) will case one collective vote for the NCI.

Meetings - The Coordinating Committee will meet at least quarterly via teleconference or videoconference to share information on planning, study progress and challenges, preliminary results and analyses in progress. Quarterly meetings will be held in February, May, August, and November. In-person meetings may be held on a yearly basis, as appropriate.

The Committee Chair will be responsible to formulate and share an agenda with attendees before each meeting. Any Committee member may propose agenda items in advance of the meeting or during the meeting as time permits. All quarterly meetings will begin with the approval of the prior meeting's minutes, and review of prior action items. New agenda items distributed in advance are reviewed next. Any tabled agenda items will be carried over to the next meeting. Minutes will be taken by DCP and distributed to all Committee members within two weeks of each meeting. Meeting minutes will reflect the name of meeting attendees, key discussions/votes that occurred, and action items that resulted from the meeting.

b. Ad Hoc Working Groups

The Coordinating Committee may establish working groups/sub-committees as needed, e.g., to address scientific and administrative issues and/or to coordinate policies, harmonize protocols, implement best practices for clinical trials conduct across sites and participating countries, coordinate regulatory approvals, etc. This decision will be made by the existing voting members of the Coordinating Committee.

Current proposed ad hoc working groups include the following groups:

- Recruitment and Retention
- HPV Testing and Screening
- Pre-cancer Treatment

c. ULACNet Clinical Trials Oversight Committee (CTOC)

The Committee will be involved in the NCI decisions about approval and initiation of individual clinical trials, oversight for the conduct of these trials, and coordination with other NCI-funded initiatives. This Committee will be chaired by the NCI DCP ULACNet Director and will have representation from scientific and programmatic staff from the NCI Division of Cancer Prevention, NCI Office of HIV/AIDS Malignancy, NCI Center for Global Health, other relevant NCI Divisions, Offices, and Centers with appropriate expertise, as well as representatives from co-funding NIH institutes such as the National Institute of Dental and Craniofacial Research (NIDCR). This

Committee will be responsible for final concurrence regarding protocol approval and initiation of individual clinical trials.

In addition, the Committee will provide recommendations to the ULACNet Partnership Center Coordinating Committee regarding oversight for the conduct of these trials, coordination of Partnership clinical trials with other relevant NCI- and NIH-funded initiatives, and other strategic aspects of the Partnership Centers Program.

The Committee may convene on an *ad hoc* basis to recommend suspension, termination, or curtailing an ongoing clinical trial in the event of unexpected/serious adverse events, substantial shortfall in participant accrual, data reporting, inadequate quality control in data collection, suboptimal clinical care of study participants, non-adherence to biohazard precautions, and other serious medical and/or regulatory issues. The Committee may also recommend other corrective actions in case of sub-optimal performance of the awardees and/or their affiliated institutions (including recommendation to restructure sub-contractual arrangements).

d. Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (HHS) grant administration regulations at 45 CFR Part 75, and other HHS, PHS, and NIH grant administration policies.

i. **PD(s)/PI(s) Primary Responsibilities**

- Defining objectives and approaches of the Partnership Center and providing leadership and coordination across clinical trial protocol teams, Core Directors, and collaborating investigators.
- Ensuring scientific integrity, productivity, governance, and fiscal accountability for the Partnership Center.
- Overseeing the Administrative and Coordinating Core and providing overall administration, coordination, communication, and management including, but not limited to, the following activities: training and study monitoring, regulatory support, submission to institutional review boards (IRBs) and institutional oversight committees, recruitment and retention efforts, convening and liaison with data safety and monitoring boards, ensuring certification of all key personnel in training on the Protection of Human Subjects and Good Clinical Practices (GCP).
- Overseeing protocol amendments/status changes, quality assurance efforts, and study monitoring.
- Coordinating efforts with the Data Management and Statistical Core Director(s) for efficient data management and statistical design and analytical aspects of each of the proposed Clinical Trials.
- Coordinating efforts with the Central Laboratory Core Director(s) for efficiently managing and coordinating acquisition and shipping of protocol-specified biological specimens (with relevant clinical data) to appropriate laboratories for testing and tumor/specimen repository for storage of specimens for future correlative laboratory studies.
- Ensuring adherence to requirements regarding investigational drug management and federally mandated regulations and protocol and performance reporting, submission of annual progress reports to the NCI that describe activities and accomplishments during the previous year of funding, and submission of timely reports of all serious and/or unexpected adverse events to the NCI and relevant regulatory agencies.
- Adhering to additional certification requirements with each submission of the Annual, Interim, and Final Research Performance Progress Report (RPPR) as outlined in the Terms of Award.
- Partnering with Co-Chairpersons of each Clinical Trial Protocol to oversee protocol

development, including study design, definition of objectives and approaches, planning, implementation, analysis, and publication of results, interpretations, and conclusions.

- Ensuring accurate and timely knowledge of the progress of each study by developing standard procedures for timely data collection and data management consistent with the more intensive data requirements and the need for rapid reporting necessary for pilot, Phase I, and Phase II prevention clinical studies.
- Ensuring protection of confidentiality of research participants at all steps in the submission and analysis of clinical trials data and ensuring the technical integrity and security of the data management systems,
- Providing NCI in a timely manner, upon the request of the NCI Program Scientist, true copies of data files and supporting documentation for all NCI-supported protocols, as well as providing to the NCI periodic study reports to include information detailing patient accrual and demographics, data timeliness, toxicity experienced by study participants, and other items including outcome data as appropriate.
- Establishing routine electronic communication with Clinical Trials site institutions to facilitate study monitoring, and to facilitate the work of the Protocol teams. Relevant communication methods include e-mail, teleconferences, video conferences, and web site postings.
- Providing mentorship and networking opportunities for new/early stage/junior investigators as well as patient advocates in clinical trials research/activities.
- Adhering to and complying with the decisions and recommendations of the NCI Clinical Trials Oversight Committee and Partnership Center Coordinating Committee to the extent consistent with applicable grant regulations.

ii. NIH Staff **Programmatic** Involvement

Above and beyond the normal stewardship role in awards, as described below:

Designated NCI Program Director(s) will have substantial involvement as Program Scientist(s). Additionally, an NCI Program Director, acting as Program Official will be responsible for the normal, scientific and programmatic stewardship of the award and will be named in the Notice of Award (NoA)

Activities of substantially involved NCI staff members will include:

- Ensuring that clinical trials proposed are within the research scope of the Partnership Center Program and relevant to the state-of-the-science, NIH/NCI priorities, resources, and availability of funding.
- Finalizing reviews of clinical trial protocols and amendments after evaluation by the NCI Clinical Trials Oversight Committee and monitoring the progress and performance of the Partnership Centers.
- Serving as a resource for scientific information on trial/study design and as scientific liaison for scientific opportunities resulting from NIH/NCI-supported research programs for facilitating appropriate collaborations.
- Evaluating and approving of clinical trial collaborations with outside organizations including review of any agreements/memoranda of understanding (MOUs) for compliance with NIH/NCI and Federal policies.
- Overseeing data management and monitoring programs for the proposed clinical trials as well as overseeing and participating as necessary in on-site auditing programs and quality assurance programs.
- Overseeing data and safety monitoring plans for the proposed Clinical Trials, and final review and approval of requests for use of any bio-specimens collected per the approved

protocol for Clinical Trials.

- Ensuring compliance with the United States Food and Drug Administration (FDA) for any relevant investigational agents and ensuring compliance with OHRP and other federal regulations for research involving human research subjects including compliance with Good Clinical Practice (GCP) guidelines: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/good-clinical-practice and https://www.fda.gov/media/93884/download
- Reviewing data collected and/or generated under this Cooperative Agreement.

iii. **Areas of Joint Responsibility Between the NCI/DCP and the Partnership Centers**

- General aspects of collaboration on study development and conduct especially with respect to compliance with federal regulations for clinical trial research, conduct of Data and Safety Monitoring Boards (DSMBs) for relevant phase 3 trials and randomized phase 2 trials will be shared between the NCI/DCP (i.e., the Funding Sponsor) and the Partnership Centers (i.e., the Study Sponsors).
    - Funding Sponsor – NCI/DCP serves as the Funding Sponsor for this Cooperative Agreement, as it is the Federal awarding agency.
    - Study Sponsors – The Partnership Centers serve as the Study Sponsors and are responsible for managing the day-to-day operations of grant-supported activities using their established controls and policies consistent with NIH requirements.

iv. Award Release

- Once the protocol has been reviewed and approved by Clinical Trials Oversight Committee, appropriate IRB approval(s) have been received and any other requirements for Human Subjects research have been submitted by the Partnership Center's Office of Sponsored Research to the NCI Grants Management Specialist, a revised NoA will be issued. All IRB approvals shouls be submitted to ULACNet@mail.nih.gov as received.

IV. ULACNet Protocol Operations

a. DCP PIO Document Management

The Division of Cancer Prevention (DCP), Protocol Information Office (PIO) is the central clearinghouse for clinical trials management within DCP. The PIO will be responsible for receiving, processing, reviewing, tracking, and obtaining approval of all protocol-related information, including concepts, revisions, protocols, amendments, and changes in protocol status. Templates for ULACNet protocol development, the Protocol Submission Worksheet, and the Study Status Update form may be found at https://prevention.cancer.gov/clinical-trials/clinical-trials-management/us-latin-american-caribbean

i. Protocol Naming Convention

Protocol naming convention will be as follows:
ULACNet - Site Number (1, 2, 3) Protocol Number (01, 02, 03)

Site Name	*Site Number*
University of California, San Francisco	1
Weill Medical College of Cornell University	2
Fred Hutchinson Cancer Research Center	3

Example: ULACNet-101
This is the name for the first protocol for UCSF.

b. Required Documents

All required documents should be sent to the DCP PIO mailbox [nci_dcp_pio@mail.nih.gov] and the ULACNet mailbox [ULACNet@mail.nih.gov].

First Protocol Submission*: (all documents must have the same date and version number on all pages)

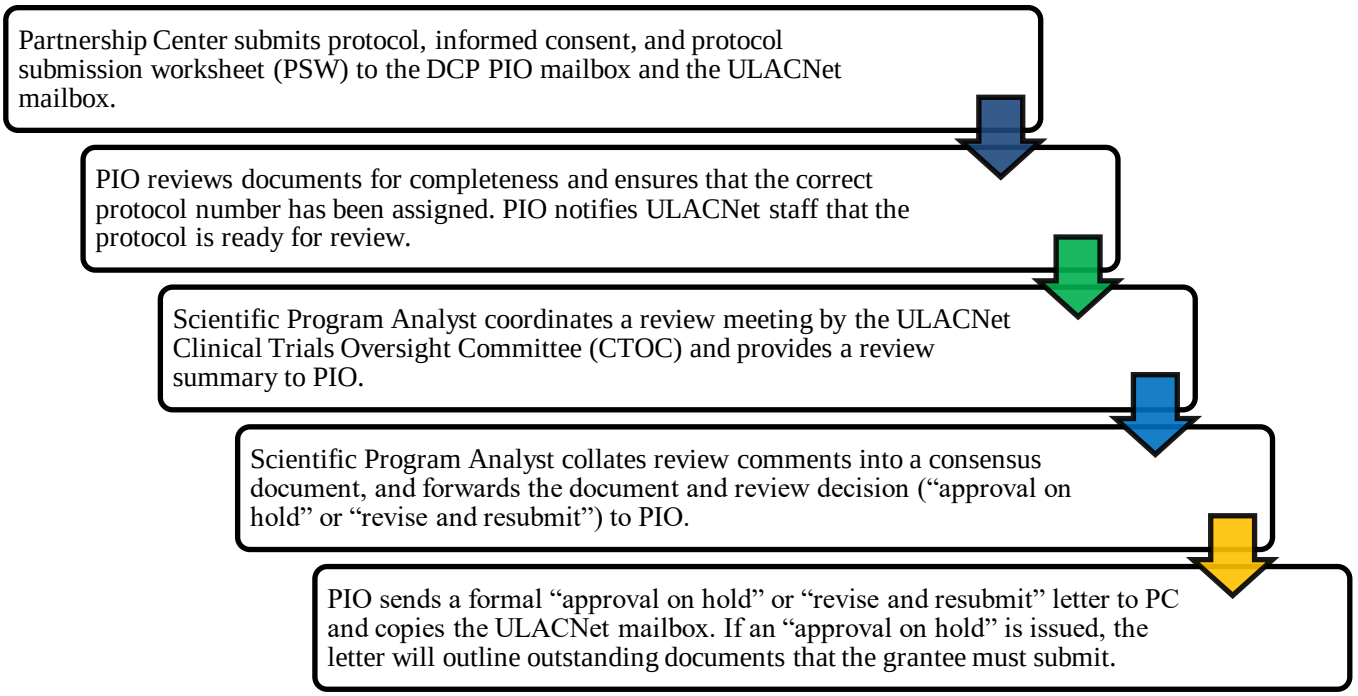
1. **Protocol Submission Worksheet (PSW)**
2. **Protocol** – must use the ULACNet-specific template and standard PIO versioning
3. **Informed Consent** – must be in English and have the study number on it

*Revised protocol submissions must contain "tracked changes" and "clean" versions of the protocol and informed consent documents as well as a cover letter explaining the changes.

Additional Required Documents:

1. **IRB Approvals** – IRB approval and/or approval from a country's regulatory authority must be received from the US-based institution and one international accrual site for the trial to be "open to accrual" (Section IV.d). For all other accruing sites, the international site IRB and/or country regulatory authority approval must be submitted to DCP before accrual begins at that site. The award prohibits expending human subject funds before IRB approval.
2. **Study Status Update Form** - required after the initial study is approved in order to document a change in study status
3. **Recruitment Materials** - collection is for recruitment repository only. They will not be translated. NCI review will not occur.

c. Protocol Submission and Review Process



d. "Open to Accrual" Requirements

Once all outstanding documents have been submitted, the PIO will issue a "final study approval/open to accrual" letter. A study can open at the first site only after all of the following have been received:

- Protocol approval from ULACNet Clinical Trials Oversight Committee
- US LAO's IRB approval or acknowledgement letter
- Letter from the Contact PI about the Partnership Center's compliance with NCI Registration and Credential Repository (RCR) requirements (as stated in Section V.a) for the first accrual site
- IRB approval or endorsement from regulatory authority responsible for clinical trial approvals for the first accrual site
- Letter from the Contact PI confirming availability of either:
    - study agent at the study site pharmacy
      OR
    - equipment and supplies for screening and diagnostic evaluations necessary for the primary study objective screening

The following are required to be submitted to NCI to open accrual at additional sites:

- IRB approval or endorsement from regulatory authority responsible for clinical trial approvals
- Site specific informed consent forms
- Letter from the Contact PI about the Partnership Center's compliance with NCI Registration and Credential Repository (RCR) requirements (as stated in Section V.a) for the first accrual site
- Letter from the Contact PI confirming availability of either:
    - study agent at the study site pharmacy
      OR
    - equipment and supplies for screening and diagnostic evaluations necessary for the primary study objective screening

e. Amendment Submission and Approval

The Partnership Center must submit all administrative and scientific amendments to the PIO via the DCP PIO mailbox. The PIO will share the amendment documents with ULACNet staff. Scientific amendments will be reviewed by the ULACNet Director and, on an ad hoc basis, by the ULACNet Clinical Trials Oversight Committee. If the amendment is approved by DCP, the PIO will notify the PC of amendment approval. Relevant IRB approvals from the LAO and the site(s) will be required to activate the amendment.

f. Submission and Review Timeline

Task	**Target Timeline (in calendar days)**
PC first submission to NCI review	21 days
Revisions and resubmission by Partnership Center*	30 days
NCI review of revised protocol to sending concurrence letter or "approval-on-hold" letter*	15 days

*Multiple rounds of revisions can occur with these target timelines.

V. Trial Reporting Requirements

a. NCI Registration and Credential Repository (RCR)

It is required for all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually: https://ctep.cancer.gov/investigatorResources/default.htm

b. Monthly Minimum Data Set (MDS)

The MDS is a collection of specified administrative, participant demographic, and adverse event data that serves as an important source of information about the ULACNet clinical trials. The Data Management Core of each PC will work with the DCP Protocol Information Office and its contractor on monthly transfer of MDS data for each clinical trial. Files should be successfully submitted by the 10th of each month. The detailed process will be described in a network SOP.

The ULACNet MDS will include the following data elements:

- DCP Protocol Number
- Submission Date
- Report Cut-off Date
- Current Trial Status
- Current Trial Status Date
- Name of Person Submitting the Data
- Submitter Telephone Number
- Submitter Email Address
- Participant Identifier
- Participant Zip Code
- Participant Country Code
- Participant Birth Date
- Participant Gender
- Participant Race
- Participant Ethnicity
- Informed Consent Date
- Screen 1
- Screen 2
- Registration Date
- Randomization Date
- Eligibility Status
- Participant Enrollment Date
- Registering Consortium
- Registering Institution
- Participant Method of Payment
- Treatment Assignment Code (TAC)
- Date Agent Started
- Agent End Date
- Off Study Date
- Off Study Reason
- Reason Off Study Other, Specify
- Adverse Event (AE) Verbatim Term
- MedDRA System Organ Class (SOC)
- CTCAE Term
- AE Grade
- AE Attribution
- Reported as a serious adverse event (SAE)?
- Event Onset Date
- Event End Date
- Dropped Due to an adverse event (AE)?
- Outcome

c. Serious Adverse Events

All serious adverse events (SAE) will be reported to NCI DCP via ULACNet@mail.nih.gov. The PC must send the initial SAE report to DCP within 24-48 hours of learning of the event. A final report including the medical monitor's assessment must be submitted when complete.

In addition, any major patient safety issues (e.g., study closure/suspension for adverse events, inappropriate randomization of patients to treatment arms) also require immediate notification to the NCI DCP via ULACNet@mail.nih.gov.

In general, for studies with these types of immediate safety issues that are under monitoring by a Data and Safety Monitoring Board (DSMB), immediate notification should be made to the DSMB/DMC Chair and NCI DCP via ULACNet@mail.nih.gov.

d. ClinicalTrials.gov Registration and Result Reporting

In an effort to make information about clinical trials widely available to the public, the US Department of Health and Human Services issued The Final Rule (42 CFR Part 11) that clarifies and expands the regulatory requirements and procedures for submitting registration and results information for certain trials to ClinicalTrials.gov, in accordance with FDAAA 801. In addition, NIH has issued a complementary policy for registering and submitting summary results information to ClinicalTrials.gov for all NIH-funded clinical trials, including those not subject to the final rule. The Partnership Center is responsible for ensuring adherence to these policies when submitting and updating ClinicalTrials.gov.

i. Trial Registration

To be compliant with the FDA Amendments Act (FDAAA) Final Rule Section 801 and NIH policies (https://www.clinicaltrials.gov/ct2/manage-recs/fdaaa), the Partnership Center is required to register each clinical trial in ClinicalTrials.gov ***within 21 days of enrollment of the first participant.***

ii. Posting Clinical Trial Protocols

The LAO is responsible for providing Clinical Trials.gov with the most recently approved protocol version (with redaction as needed), including the informed consent, for posting.to the public ClinicalTrials.gov website. Protocols must be submitted to ClinicalTrials.gov ***no later than 12 months after the primary completion date.***

The LAOs will be responsible for working with pharmaceutical partners, as appropriate, to determine if any proprietary information needs to be redacted prior to sending it to ClinicalTrials.gov for public posting.

iii. Posting Informed Consent Document

The Partnership Center will post the most recent IRB-approved model consent form to ClinicalTrials.gov ***within 60 days of the study status changing to "Closed to Accrual and Treatment."***

iv. Clinical Trial Results Reporting

The Partnership Center must submit clinical trial results via the ClinicalTrials.gov Protocol Registration and Results System Information Website (https://register.clinicaltrials.gov) in accordance with network policies and procedures. The standard submission deadline for results information is ***no later than 12 months after the trial's primary completion date***. NIH expects registration of all trials whether required under the law or not. For more information, see http://grants.nih.gov/ClinicalTrials_fdaaa/.

e. Resource Sharing Plans

i. Data Sharing Policy

The PCs are responsible for following their approved plan for sharing research data. Information on the NIH policy regarding sharing research data can be found on the NIH website at http://grants.nih.gov/grants/policy/data_sharing. Per this policy, requests for data will only be considered once the primary study analyses have been published.

ii. Biospecimen Sharing Policy

Partnership Centers are required to follow NCI/DCP policy regarding review of requests for use of banked biospecimens collected in association with ULACNet trials that it leads, which requires approval by a designated review committee. Partnership Centers should also have plans in place regarding resource sharing, as appropriate for the clinical research it conducts.

iii. Genomic Data Sharing Plan

For each ULACNet study that generates large-scale human or non-human genomic data, the Partnership Center is responsible for submitting to the DCP PIO:

1) The signed Genomic Data Sharing Plan (GDSP) and the provisional institutional approval with the first protocol iteration

   i. The PIO will forward the signed GDSP and provisional institutional approval to the DCP ULACNet

   ii. The PIO will forward the signed GDSP, provisional institutional approval, and the concept or protocol to the DCP GDS representative

2) The final completed and signed Institutional Certificate after IRB approval

   i. The PIO will forward the final institutional approval to the ULACNet staff. ULACNet staff will ensure that these documents are on file with the NCI Office of Grants Administration.

   ii. No funds may be drawn down from the payment management system and no obligations may be made against federal funds for any activities involving the generation of large scale human genomic data until such time that the recipient has received official notification from the NIH Grants Management Official indicating acceptance of the final Institutional Certification and removing this restriction.

NOTE: *Final DCP study approval will not be delayed for receipt of Final Institutional Certification*
NIH Genomic Data Sharing Policy
https://osp.od.nih.gov/wp-content/uploads/NIH_GDS_Policy.pdf

About the Genomic Data Sharing (GDS) Policy
https://datascience.cancer.gov/data-sharing/genomic-data-sharing/about-the-genomic-data-sharing-policy

Information for External Grantees Submitting Genomic Data with step-by-step instructions
https://datascience.cancer.gov/data-sharing/genomic-data-sharing/extramural-grantees

Genomic Data Sharing Plan (GDSP) template
https://datascience.cancer.gov/sites/default/files/2019-02/nci-dsp.pdf

Institutional Certificate template
https://osp.od.nih.gov/scientific-sharing/institutional-certifications/

f. Data Rights

NCI will have access to all data generated under this cooperative agreement and may periodically review the data. The awardee will retain custody and primary rights to the data consistent with current HHS, Public Health Service (PHS), and NIH policies.

Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to government rights of access consistent with current HHS, PHS, NIH, and NCI policies and within the limits of any accepted binding NCI/NIH collaborative agreements with biotechnology and pharmaceutical partners and as governed by NCI-approved Data Sharing Plans and NCI-approved review for use of biospecimens collected in association with ULACNet trials/studies.

g. Data and Safety Monitoring Requirements

The NIH policy for data and safety monitoring requires oversight and monitoring of all NIH-conducted or NIH-supported clinical trials to ensure the safety of participants and the validity and integrity of the data. Further information concerning these requirements is found at https://grants.nih.gov/policy/humansubjects/policies-and-regulations/data-safety.htm

i. Data and Safety Monitoring Plan

Each ULACNet PC must adhere to their approved Data and Safety Monitoring Plan including Data and Safety Monitoring Board (DSMB) oversight of relevant network clinical trials. The NIH policies on data and safety monitoring specify that the level and frequency of monitoring should be commensurate with the risks. A DCP Program Official will serve as non-voting (Ex officio) representative to the DSMB. Sites should include ULACNet@mail.nih.gov on Data and Safety Monitoring Board meeting schedules/invitations.

ii. Clinical Site Monitoring of Each Accruing Organization

For each trial, the ULACNet Partnership Center must perform routine monitoring of each accruing organization throughout the conduct of the study. Overall areas of review are below outlined.

1. Review of all regulatory documents and assurance of compliance with all relevant regulatory requirements
2. Review of site operations compliance (e.g., compliance with federal regulations/NIH policies for Human Subjects Protection, adequate resource to conduct study, staff training, secure study record storage, research specimen management)
3. Pharmacy review (e.g., investigational agent is secure; agent properly received, stored and inventoried; agent dispensed according to protocol)
4. Review of participant records (e.g., each participant signed correct informed consent version, and met all inclusion/exclusion criteria; review of all SAEs, protocol compliance, accurate/timely collection of study accrual data)
5. Accural metrics (e.g. assessment of accrual pace, challenges, mitigation plans)

All monitoring reports sent to PC from clinical sites should be forwarded to NCI via ULACNet@mail.nih.gov.

iii. Record Retention and Access

Awardees generally must retain financial and programmatic records, supporting documents, statistical records, and all other records that are required by the terms of a grant, or may reasonably be considered pertinent to a grant, for a period of 3 years from the date the annual FFR is submitted.

h. Related Documents

Other study related documents are available at: https://prevention.cancer.gov/clinical-trials/clinical-trials-management/us-latin-american-caribbean including the Protocol Template and Informed Consent Template.

VI. Key Definitions for these Guidelines

- **Alignment with NIH priority research areas:** The NIH has developed a series of guidelines to determine if a research project is ALIGNED with NIH priorities and eligible to receive support with HIV/AIDS-designated funds. The guidelines are not used to assess the scientific or technical merit of a research project. A description of priority topics and examples are provided in NOT-OD-20-018.
- **Accrued Participant:** an individual who has completed the informed consent process, has been deemed eligible through all levels of the screening process, and has started the trial intervention (e.g., actually received the agent and/or intervention to be tested)
- **Clinical trials:** The NIH has clarified its definition of a clinical trial in NOT-OD-15-015. A clinical trial is defined as 'research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes'.
- **Latin American and Caribbean (LAC) region:** In the context of this network, the LAC region refers to all countries referred as being in the Latin American and Caribbean region in the World Bank classification system http://data.worldbank.org/about/country-classifications/country-and-lending-groups.
- **Low- and Middle-Income Countries (LMICs):** In the context of this network, LMICs refer to countries classified according to Gross National Income (GNI) per capita as "low-income," "lower-middle-income," and "upper-middle-income" in the World Bank classification system http://data.worldbank.org/about/country-classifications/country-and-lending-groups.
- **Program Director/Principal Investigator**: the person in charge of a ULACNet Partnership Center
- **ULACNet Partnership Center:** a collaboration between a research institution in the United States as the Lead Academic Organization (LAO) and Affiliate Organizations (AOs) in the US and LMICs in the LAC region.

VII. Important Abbreviations

ABBREVIATION	FULL TERM
AIDS	Acquired Immune Deficiency Syndrome
AO	Affiliate Organization
CFR	Code of Federal Regulations
CTRP	Clinical Trials Reporting Program
CTRO	Clinical Trials Reporting Office
CTOC	Clinical Trials Oversight Committee
DCP	Division of Cancer Prevention
FOA	Funding Opportunity Announcement
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMS	Grants Management Specialist
HHS	US Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSP	Human Subjects Protection
IND	Investigational New Drug Application
IRB	Institutional Review Board
LAC	Latin America and Caribbean
LAO	Lead Academic Organization
LMIC	Low- and Middle-Income Countries
MOU	Memoranda of Understanding
NCI	National Cancer Institute
NIH	National Institutes of Health
OD	Office of the Director at the NCI
OHRP	Office for Human Research Protections
PAHO	Pan American Health Organization
PC	Partnership Center

PHS	Public Health Service
PD/PI	Program Director(s)/Principal Investigator(s)
PIO	Protocol and Information Office
RCR	Registration and Credential Repository
ULACNet	US-Latin American-Caribbean HIV/HPV Cancer Prevention Clinical Trials Network (ULACNet)