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



**National Cancer Institute**

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

**Program Guidelines**

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**Division of Cancer Prevention**

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# Introduction

## 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) via a U54 Partnership Centers Cooperative Agreement mechanism, focuses on developing evidence to improve and optimize approaches for prevention of Human Papilomavirus (HPV)-related cancers in people living with Human Immunodeficency Virus (HIV) in low- and middle-income countries (LMICs) in the Latin American and Caribbean (LAC) region. 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](https://grants.nih.gov/grants/guide/rfa-files/rfa-ca-18-018.html).

## ULACNet Background, Purpose, and Objectives

### 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 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.

### 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 (PLWH).

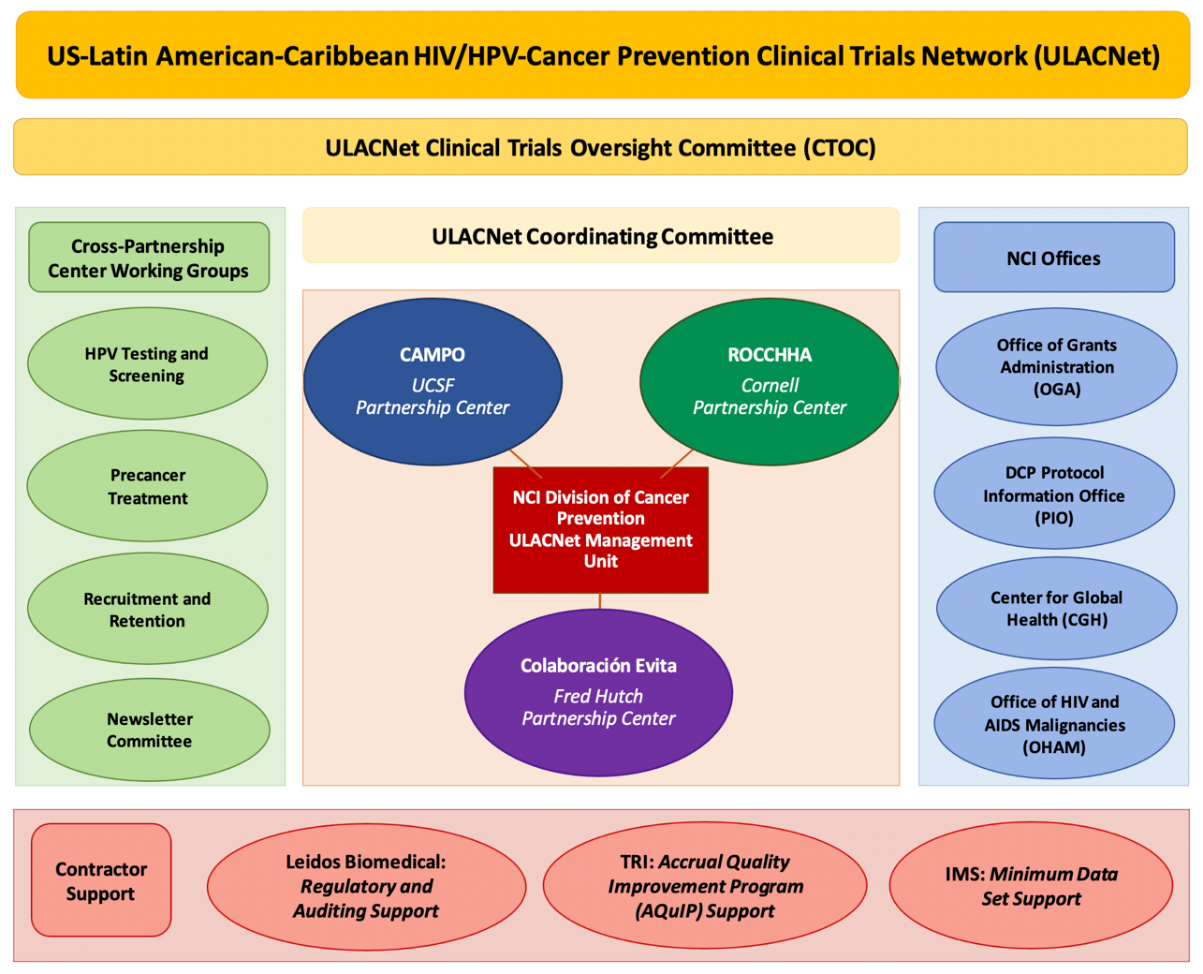
### Objectives

The ULACNet Partnership Centers will:

* propose, develop, and conduct highly meritorious clinical trials focused on prevention of HPV-related cancers in PLWH. These clinical trials will be conducted jointly by the US 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 PLWH.

# Organizational Structure for ULACNet

## Network Stucture



## Structure of Each ULACNet U54 Partnership Center

**Administrative and Coordinating Core**

**Clinical Trials Program**

**Trial 1 Team**

**US PI(s)**

**LAC PI(s)**

**Trial 2 Team**

**US PI(s)**

**LAC PI(s)**

**Central Laboratory Core**

**Trial 3 Team**

**US PI(s)**

**LAC PI(s)**

**Data Management**

**and Statistical Core**

## Network Collaborators

|  |  |  |  |
| --- | --- | --- | --- |
| **Partnership Center** | **CAMPO** | **ROCCHHA** | **Colaboración Evita** |

**Footnotes:**

**CAMPO** = CAlifornia-Mexico-Puerto RicO Collaboration for the Prevention of HPV-related Cancer in People Living with HIV

**ROCCHHA** = Research on Oral and Cervical Cancer, HPV and HIV in the Americas

\*Indicates AOs that are accruing study participants

## 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 LMICs in the LAC region. Each Partnership Center consists of the following components (diagram II.b.):

i. Administrative and Coordinating Core

ii. Data Management and Statistical Core

iii. Central Laboratory Core

iv. Clinical Trials Program

### 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 NCI/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)*

### 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

### 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

### 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](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-018.html)). 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 Institutional Review Board (IRB) approval(s) on file and be reviewed and approved by the ULACNet CTOC before activation through the Partnership Center.

Diagram of the three scientific focus areas of the clinical trials in ULACNet:
Area 1: Optomizing dosing and delivery and evaluating new indications for HPV prophylactic vaccines
Area 2: Evaluating new biomarkers and technologies for improving accuracy of cervical and anogenetical cancer screening and triage
Area 3: Evaluating novel non-excisional treatment approaches for HPV-related precancers


*Figure 1. NCI-supported research areas on optimization of clinical prevention interventions for PLWH*

# Program Governance

## 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 Project Scientist) will cast 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 NCI/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.

## Cross Partnership Center 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
* Precancer Treatment
* Newsletter Committee

## 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 and other relevant NCI Divisions, Offices, and Centers with appropriate expertise (such as the NCI Office of HIV/AIDS Malignancy, NCI Center for Global Health, etc.) , 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).

## 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.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities. Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

### ****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 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 ULACNet CTOC and Coordinating Committee to the extent consistent with applicable grant regulations.

### ****NIH Staff Programmatic Involvement****

NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards. The ULACNet Director will be a designated NCI Program Director with substantial involvement as Project Scientist. Other NCI staff (intramural or extramural) may have substantial involvement as Project Scientists. 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 award notice.

Activities of substantially involved NCI staff members will include:

* Ensuring that clinical trials proposed are within the research scope of the Partnership Centers 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 ULACNet 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 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.

### ****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 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.

# ULACNet Protocol Operations

## NCI/DCP PIO Document Management

The NCI/DCP Protocol Information Office (PIO) is the central clearinghouse for clinical trials management within NCI/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 Protocol Status Update form may be found at <https://prevention.cancer.gov/clinical-trials/clinical-trials-management/us-latin-american-caribbean>

### Protocol Naming Convention

Protocol naming convention will be using a three digit suffix to “ULACNet-” as follows:

* The first digit will be reflecting the ULACNet Partnership Center Number (1, 2, 3) as follows: 1=CAMPO, 2= ROCHHAA, 3= Colaboración Evita
* The second and third digits reflecting the sequential protocol number, e.g., 01, 02, 03, etc.

Example: “ULACNet-101” is the name for the first protocol for CAMPO.

Note: Ancillary Protocols will be named with suffixes of “-A”, “-B” etc. after the primary number (e.g., “ULACNet-101-A”)

## Required Documents

All required documents should be sent to the NCI/DCP PIO mailbox [[nci\_dcp\_pio@mail.nih.gov](mailto:nci_dcp_pio@mail.nih.gov)] and the ULACNet mailbox [[ULACNet@mail.nih.gov](mailto: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 change memo 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 NCI/DCP before accrual begins at that site. The award prohibits expending human subject funds before IRB approval.

1. **Protocol Status Update Form** - required after the initial study is approved in order to document a change in study status
2. **Recruitment Materials** - collection is for recruitment repository only. They will not be translated. NCI review will not occur.

## Protocol Submission and Review Process

## “Open to Accrual” Requirements

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

* Protocol approval from ULACNet CTOC
* US LAO’s IRB approval or acknowledgement letter
* IRB approval or endorsement from regulatory authority responsible for clinical trial approvals for the first accrual site
* In-country approval (if applicable, refer to <https://clinregs.niaid.nih.gov/>)
* IND approval (if applicable)
* Confirmation that NCI Registration and Credential Repository (RCR) requirements and Delegation of Task Logs (DTLs) are complete for the first accrual site (as stated in Section V.a)
* Letter from the Contact PI confirming availability of either (as per protocol requirements):
  + study agent at the study site pharmacy

AND/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 receive a “site activiation letter” to start accruing to the study at additional sites:

* IRB approval or endorsement from regulatory authority responsible for clinical trial approvals
* In-country approval (if applicable, refer to <https://clinregs.niaid.nih.gov/>)
* Site specific informed consent forms (if different from first site)
* Confirmation that NCI RCR requirements and DTLs are complete for the accrual site (as stated in Section V.a)
* 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

## Award Release

Once the protocol has been reviewed and approved by ULACNet 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.

## Study Specific Monitoring Plans

A draft monitoring plan written by the LAOs or their selected CRO must be submitted to NCI/DCP via the NCI/DCP PIO no later than 30-days after a study is given approval on hold. Final study approval will not be granted unless a draft monitoring plan has been submitted. An approved monitoring plan should be in place no later than 30-days after the study is initiated. Refer to the *Study-Specific Monitoring Plan Guidance Document*on the ULACNet website for more information.

## Amendment Submission and Approval

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

## Submission and Review Timeline

|  |  |
| --- | --- |
| **Task** | **Target Timeline**  **(in calendar days)** |
| Partnership Center first submission to NCI review | 30 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.*

## Ancillary Studies

In ULACNet, a study deemed as an ‘Ancillary Study’ will have the following characteristics:

* must extend knowledge of diseases being studied by parent study investigators under a defined protocol, or study diseases and conditions outside of the original scope of the parent study but within the research areas and mission of NCI
* must abide by the procedures established by the parent study
* may focus on additional data or sample collection from human subjects,
* may not interfere with the primary objectives of the parent study

Note: An Ancillary Study Protocol may focus on a study that may—in and of itself-- not meet the NIH definition of a [clinical trial](file:///C:\Users\housem\Desktop\clinical%20trial) (see: <https://grants.nih.gov/policy/clinical-trials/definition.htm>), although it will be nested within (or linked to) the parent study that, by virtue of being supported in ULACNet, will be a NIH-defined clinical trial.

The process for submitting ancillary protocols is the same as other studies. There will be a scientific and administrative review by NCI/DCP and by the CTOC if necessary. Refer to the ULACNet Protocol Template for Ancillary Studies for more information.

# Trial Reporting Requirements

## Delegation of Tasks Logs (DTL) and NCI Registration and Credential Repository (RCR)

A DTL is a document used to show which study tasks a site principal investigator (PI) has delegated to the personnel working on a clinical research study at a specific accruing clinical research site at any given time. The DTL must be updated every time there is a change in personnel or personnel delegated study tasks. Each accruing site must complete a DTL.

All personnel listed on a ULACNet DTL or protocol face sheet should register in RCR. They must renew their registration annually: <https://ctep.cancer.gov/investigatorResources/default.htm>

A guidance document on DTL and RCR is available on the ULACNet website. No PI signature page is required for ULACNet studies because the 1572 forms and DTL/RCR will document PI oversight responsibilities.

## 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 Partnership Center will work with the NCI/DCP PIO 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 is described in a network SOP. The ULACNet MDS will include the following data elements:

|  |  |
| --- | --- |
| * NCI/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 sex * 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 |

## Treatment Assignment Code (TAC) / Treatment Assignment Description (TAD)

For MDS reporting purposes, each study will utilize Treatment Assignment Codes (TAC). The TAC is a coded value representing a treatment assignment that is uniformly administered to a group of study participants for separate statistical analysis. A TAC will be assigned to each unique study arm or dose level utilized in a study to uniformly group participants. The study PI and study statistician will work with the NCI/DCP PIO, and NCI Scientific Staff to develop TACs and Treatment Assignment Descriptions (TAD) for each study. Below is an example of a TAC and TAD for a study.

|  |  |
| --- | --- |
| **Treatment Assignment Code (TAC)** | **Treatment Assignment Description (TAD)** |
| TAC-0 | Signed informed consent and before intervention |
| TAC-1 | Lisinopril (10mg) / Placebo 1 tablet PO daily x 24 weeks |

## Serious Adverse Events

All serious adverse events (SAE) will be reported to NCI/DCP via [ULACNet@mail.nih.gov](mailto:ULACNet@mail.nih.gov). The Partnership Center must send the initial SAE report to NCI/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](mailto: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](mailto:ULACNet@mail.nih.gov).

## Protocol Deviations

ULACNet sites are responsible for reporting all protocol deviations to the Partnership Center as the study sponsor for regulatory purposes. The Partnership Center is responsible for quality assurance efforts and study monitoring, including oversight of major or minor protocol deviations, as well as any relevant reporting of unanticipated problems and/or serious or continuing non-compliance to the institutional ethics committees/IRBs. NCI/DCP should also receive a copy of any reports for unanticipated problems or serious or continuing non-compliance.

## NCI/DCP Accrual Quality Improvement Program (AQuIP)

The NCI/DCP initiated its comprehensive Accrual Quality Improvement Program (AQuIP) to reduce the likelihood of accrual delays. The overall goals of AQuIP are to support efficient accrual to ongoing studies, and to improve the design and execution of future studies.

In order to inform the analysis of recruitment efforts and to identify areas for improvement, thorough documentation about each study, the participants, the recruitment strategies, and accrual barriers are recorded. Overarching study events that may positively or negatively impact accrual (e.g., new staff hired, drug shipment delay, etc.) will be recorded by the LAO on the Recruitment Journal Study Events template. In addition, participant level information including recruitment strategies used, and whether or not the participant signs consent or starts study intervention will be recorded by each Accruing Organization on the AQuIP Accrual Report template.

Both the Study Journal, and AQuIP Accrual Report(s) are due to the NCI/DCP HelpDesk ([DCPhelpdesk@dcpais.com](mailto:DCPhelpdesk@dcpais.com)) on the 10th of each month. These data will be used to generate a cumulative Accrual Zone Monitoring Report (ZMR), which will be sent to the LAO and AOs by the end of the month. The ZMR is a color-coded accrual achievement graph that provides a visualization of the actual accrual rates compared to the projected accrual rates.

The Recruitment Journal Study Events template (English, only), and the English, Portuguese, and Spanish versions of the AQuIP Accrual Report Training Webinar and the AQuIP Accrual Report Template and are available at <https://prevention.cancer.gov/clinical-trials/clinical-trials-management/ulacnet-instructions-forms>

## 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 FDA Amendments Act (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.

### Trial Registration

To be compliant with the 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.***

### 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.

### 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.”***

### 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/.>

**All submitted information to clinicaltrials.gov must be updated at least annually if there are changes to report.**

## Resource Sharing Plans

### Data Sharing Policy

The Partnership Centers 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.

### 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.

### 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 NCI/DCP PIO:

1. The signed Genomic Data Sharing Plan (GDSP) and the provisional institutional approval with the first protocol iteration
   1. The PIO will forward the signed GDSP and provisional institutional approval to the NCI/DCP ULACNet mailbox
   2. The PIO will forward the signed GDSP, provisional institutional approval, and the concept or protocol to the NCI/DCP GDS representative
2. The final completed and signed Institutional Certificate after IRB approval
   1. 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.
   2. 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 NCI/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/>

## 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.

## 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>

### Data and Safety Monitoring Plan

Each ULACNet Partnerhip Center must adhere to their approved Data and Safety Monitoring Plan including 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. NCI/DCP staff may participate as non-voting members in DSMB meetings. Sites should include [ULACNet@mail.nih.gov](mailto:ULACNet@mail.nih.gov) on DSMB meeting schedules/invitations.

### 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 Partnership Centers from clinical sites should be forwarded to NCI/DCP via [ULACNet@mail.nih.gov](mailto:ULACNet@mail.nih.gov).

## 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.

## Related Documents

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

# 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](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-018.html).
* **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](https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html). 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>.
* **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.

# Important Abbreviations

|  |  |
| --- | --- |
| **ABBREVIATION** | **FULL TERM** |
| AIDS | Acquired Immune Deficiency Syndrome |
| AO | Affiliate Organization |
| CFR | Code of Federal Regulations |
| CRO | Contract Research Organization |
| 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 NIH |
| 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 |

# Document Submission Checklists

|  |  |  |  |
| --- | --- | --- | --- |
| **Documents** | **ULACNet Mailbox**  [ULACNet@mail.nih.gov](mailto:ULACNet@mail.nih.gov) | **PIO Mailbox**  [nci\_dcp\_pio@mail.nih.gov](mailto:nci_dcp_pio@mail.nih.gov) | **FNLCR/Leidos**  [**CMRPDDCPULACNetProjectTeam@mail.nih.gov**](mailto:CMRPDDCPULACNetProjectTeam@mail.nih.gov) |
| Protocol submissions | x | x |  |
| IRB and country approvals |  |  | x |
| IND paperwork |  |  | x |
| RCR/DTL |  |  | x |
| Letter confirming study drug and/or screening equipment |  |  | x |
| Protocol status update form |  | x |  |
| Serious adverse events (SAE) notifications | x |  |  |
| Study-specific monitoring plans |  | x |  |
| Report of Serious and Continuing Non-Compliance (SCNC) | x |  |  |
| Report of Unanticipated Problems (UPs) | x |  |  |
|  |  |  |  |