HIV/Cervical Cancer Prevention 'CASCADE' Clinical Trials Network

Program Guidelines

Version 1.0

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I. Introduction to the CASCADE Program Guidelines

NCI's HIV/Cervical Cancer Prevention 'CASCADE' Clinical Trials Network ('CASCADE') is a cooperative agreement-funded program focused on pragmatic clinical trials to optimize the cervical cancer screening, management, and precancer treatment cascade for women living with HIV. 'CASCADE' network clinical trials focus on evaluating the clinical effectiveness of prevention interventions in intended-use environments while gathering crucial information to inform implementation and scale-up. The 'CASCADE' network is composed of three types of organizational units (research bases, clinical sites, and coordinating center) working collaboratively and in partnership with the NCI to design and conduct pragmatic clinical trials with hybrid effectiveness-implementation designs, both in resource-constrained settings in low- and middle-income countries (LMICs) as well as in areas of healthcare disparities within the United States.

This document provides a high-level overview about the CASCADE network, and provides an overview of the organizational structure of the network, including composition and responsibilities of the various functional elements including the Steering Committees, Protocol Teams, and Working Groups. The document also provides an overview of the roles and responsibilities of NCI staff as part of this Cooperative Agreement-funded network. It also provides a broad and high-level overview of the Concept and Protocol Review procedures for CASCADE network clinical trials and lists various elements of the Clinical Trials Conduct and Oversight aspects. Detailed descriptions will appear in the CASCADE Network Manual of Standard Operating Procedures (M-SOP) to be developed by the CASCADE Network Coordinating Center (CNCC) that will be reviewed and approved by the CASCADE Network Steering Committee. These Guidelines are intended to be used as a resource for the network and meant to supplement instructions from the Funding Opportunity Announcements (FOAs) (RFA-CA-21-045, RFA-CA-21-046 , RFA-CA-21-047, and RFA-CA-22-051).

II. Background and Overall Goals of the 'CASCADE' Network

a. CASCADE: Background

Cervical cancer is a highly preventable malignancy, yet it is not fully prevented. Globally, there are estimated to be over 604,000 new diagnoses and over 340,000 deaths due to cervical cancer every year. Despite significant advances in the understanding of human papillomavirus (HPV)-associated etiology and pathogenesis of cervical cancer, as well as the availability of the means of both primary prevention (HPV vaccines) and secondary prevention (screening and treatment of precancerous lesions), millions of women still lack access to such lifesaving healthcare. Resource-constrained settings in low- and middle-income countries (LMICs) shoulder the vast majority of cervical cancer cases and cancer deaths globally. Following substantial reductions in cervical cancer incidence rates in the last half of the twentieth century, rates in the United States (US) have now plateaued for the past two decades, with over 13,000 women continuing to be newly diagnosed with, and over 5,700 women dying annually of this eminently preventable malignancy. Over half of the new cervical cancer cases in the US are among women who have never been screened or who are infrequently screened, reflecting barriers presented by healthcare, socioeconomic, racial/ethnic disparities, and geographic inaccessibility among other factors.

People living with HIV (PLWH) are at high risk for several malignancies, especially HPV-mediated cancers that are refractory to the immune restorative effects of combination antiretroviral therapy. HPV-associated cancers, especially cervical cancer, are significantly more common among women

living with HIV (WLWH) than in the general population. WLWH have a higher risk for acquisition, persistence, and progression of cervical HPV to precancerous lesions, which in the absence of effective screening and treatment, can progress to invasive cancer at 5-6 times higher rates than women without HIV.

The massive global mobilization of humanitarian resources spanning over the past couple of decades, especially through initiatives such as the US President's Emergency Plan for AIDS Relief (PEPFAR), has resulted in millions of PLWH in LMICs are now accessing affordable combination antiretroviral therapy (ART), and consequently living longer lives. Yet, their risk for cervical cancer continues unabated in the absence of effective screening and treatment services. The lack of such services has prompted several efforts funded by PEPFAR and several public, private, and philanthropic sector agencies to increase access to cervical cancer prevention services, especially within/linked to the clinics and facilities where WLWH routinely access HIV/AIDS care and treatment services. In addition, the World Health Organization (WHO), with the endorsement of 194 countries including the United States, has launched a global initiative to accelerate progress towards the elimination of cervical cancer as a public health problem.

Several approaches to improve efficiency, reduce costs, and facilitate the scale-up of innovations for cervical cancer preventive services have been explored. The focus on evaluating improvements in the implementation of HPV vaccination via a single dose schedule will likely have a significant impact over the next few decades. Yet, prophylactic HPV vaccination will have limited or no impact in women already infected with HPV; therefore, it is still important to focus on improving screening and treatment in the near and intermediate-term future in order to prevent disease and save lives.

In most implementation programs in low-and middle-income country settings, cervical cancer screening methods use low-cost but poorly sensitive approaches such as naked-eye visual inspection with acetic acid (VIA), a point of care clinical test that despite having limited accuracy continues to be used since it can facilitate linkages to same-visit precancer treatment or referral decisions. Treatment of precancerous lesions, wherever possible in a single visit, is conducted by ablative approaches such as cryotherapy or thermal ablation, and women with ablation-ineligible lesions are referred to tertiary facilities for excisional treatment of lesions. Management of screen-detected cancers and late-stage cancers (usual presentation in the absence of cervical cancer prevention programs) is still a major challenge, although efforts are underway to expand access to radiation therapy and build and sustain capacity for cancer surgery, chemotherapy, and palliative care services.

In the US, healthcare, socioeconomic, and racial/ethnic disparities are prominent features influencing the burden patterns of both HIV/AIDS and cervical cancer. Among WLWH, who represent a quarter of all persons living with HIV in the US, women of color, particularly Black women, represent the majority of new infections among women. And despite the widespread availability of combination antiretroviral therapy covered by both private insurance and Medicaid, a large fraction (up to 40%) of persons with HIV in the US is not virally suppressed (far short of the 95% target envisioned by the 'Ending the HIV Epidemic' plan targets), and therefore remain at much higher risk of HIV-associated co-infections and co-morbidities. Also, approximately one in five WLWH do not receive recommended cervical cancer screening, especially older women, women from racial/ethnic minorities, those from the low socioeconomic status/educational attainment, and those with low CD4+ counts. Pap smear screening is still a front-line screening approach, although HPV/Pap co-testing, as well as primary screening with HPV, have been recommended for age-

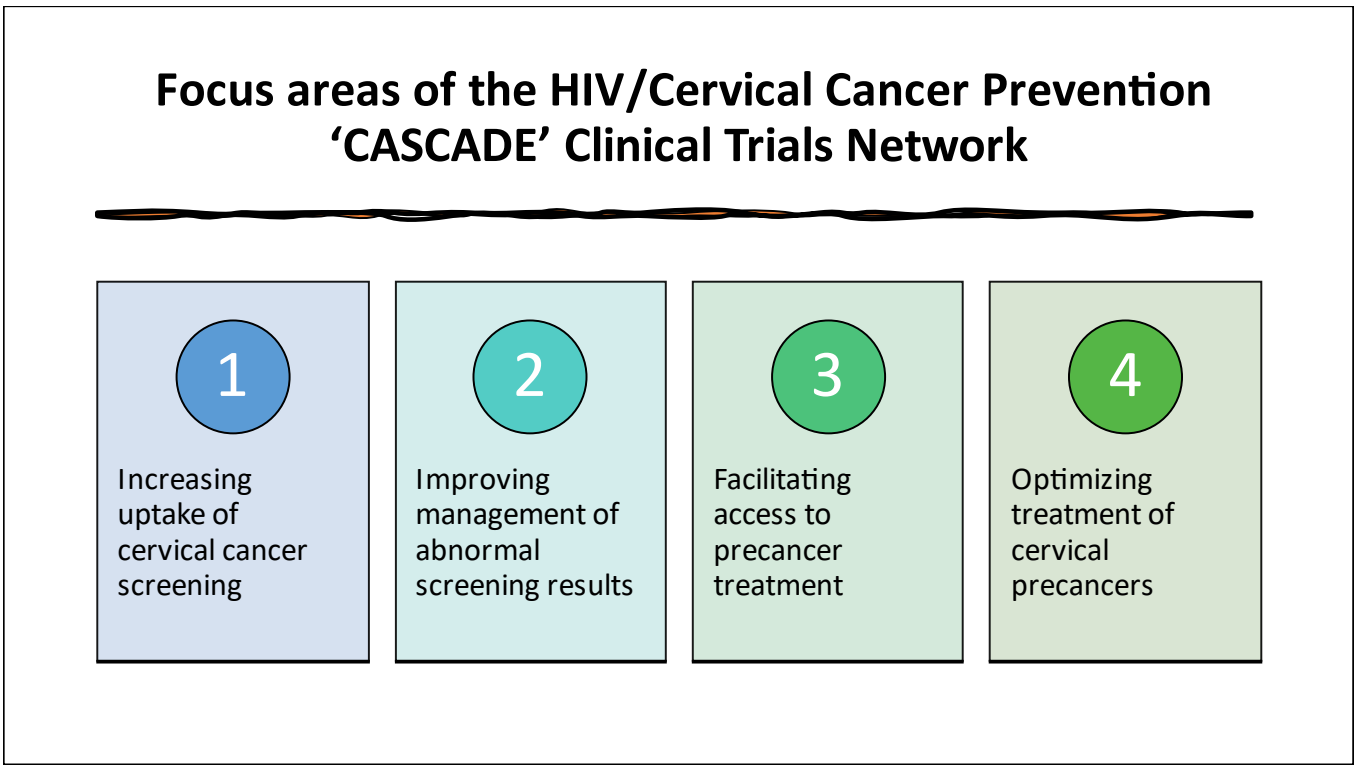
appropriate groups to lengthen the intervals of screening. Lack of FDA approval for self-sampling-based HPV testing remains a major barrier to increasing access to HPV-based screening (and is being addressed by the NCI 'Last Mile' initiative), but whether and how will self-sampling be effectively implemented as a strategy for HPV-based primary screening for WLWH has not been extensively evaluated.

Regardless of the setting, incidence rates of cervical cancer can be significantly impacted only if the entire cascade of steps/events in the pathway of accessing screening to completing treatment and follow-up are addressed. The mere availability of screening tools is not a guarantee that women will access these services, undergo the recommended screening procedures, return to receive their screening results, receive appropriately recommended precancer treatment, and complete the recommended follow-up visits. These steps in the cascade can be impacted significantly for WLWH. For example, in many settings in LMICs, with the overlaying stigma around HIV/AIDS clinic attendance and care-seeking, WLWH are reluctant to access other 'wrap around' services like cervical cancer screening, and are less likely to return for treatment visits, especially if these are not offered as part of a single visit program. Furthermore, both in the US and LMICs, WLWH have a high recurrence rate after cervical precancer treatment, so optimizing the effectiveness of these interventions is critical to reduce the burden and long-term adverse sequelae of repeated cervical treatment procedures. Finally, as the COVID-19 pandemic continues to adversely impact the utilization of cervical cancer prevention interventions both in the US and globally, it remains important to evaluate innovations in overcoming barriers to access and improve upon cost-effective clinical care delivery in screening and precancer treatment.

b. Overall Goals of the 'CASCADE' Clinical Trials Network

The 'CASCADE' Network will conduct pragmatic clinical trials evaluating the effectiveness of clinically proven interventions in intended-use settings with a goal to optimize the cervical cancer screening, management, and precancer treatment cascade for women living with HIV. The 'CASCADE' Network will have a major focus on resource constrained settings in LMICs but will also include studies addressing health disparities within the US, all with a goal to generate evidence to refine clinical practice guidelines and improve implementation of cervical cancer prevention and control programs. The 'CASCADE' Network will build on the momentum stimulated by two developments in recent years: (i) significant advances in key catalytic technologies (such as point-of-care visual and molecular screening approaches and multiple portable ablative and excisional precancer treatment devices) and acceleration of regulatory pathways (such as imminent approvals for self-sampling for HPV-based primary screening), and (ii) renewed impetus on bilateral and multilateral initiatives on cervical cancer screening and treatment (such as the PEPFAR 'Go Further' HIV-Cervical Cancer Partnership expansion in high burden countries, and the World Health Organization's Global Cervical Cancer Elimination Initiative).

The 'CASCADE' Network clinical trials will focus on measurement of clinical effectiveness of interventions in intended use settings while gathering crucial information informing the implementation and scale-up of such interventions across the cascade of screening and precancer treatment for WLWH. Such 'hybrid effectiveness-implementation' designs will primarily focus on clinical effectiveness endpoints such as HPV positivity rates and/or precancer detection/incidence/recurrence rates, and will secondarily gather data on implementation-informing aspects such as costs, acceptability, and intervention fidelity, while studying implementation strategy.



c. Research Focus Areas

There are four primary scientific research focus areas of clinical trials in the 'CASCADE' Network. 'CASCADE' Clinical trials will focus on scientific questions focused on clinical dilemmas, operational aspects, and comparative effectiveness. The four research areas and examples of outstanding research questions are listed below:

Area 1: Increasing screening uptake: Given the complexity and evolution in clinical care delivery for women with HIV, there is a need for developing innovative approaches that balance the need for maximizing the sensitivity for precancer detection while balancing costs and efficiency in screening. Clinical trials to evaluate such approaches may compare patient-targeted strategies of HPV self-sampling for increasing access (e.g., self-sampling during HIV clinic visits, home-based sampling by targeted outreach via navigators/mobile Health (mHealth) approaches, camp-based approaches, or door-to-door 'campaign' coverage) versus current local clinic-visit based standards of care (relying on VIA or cytology). Outcomes measures may include differences in cervical precancer detection rate (a clinical effectiveness metric), while also collecting information on program costs (such as costs for transitioning from current standards to primary self-sampling-based strategies), acceptability of newer approaches, and system-level barriers and facilitators all of which may provide key evidence to inform setting-specific program implementation.

Area 2: Improving management of screen positives: WLWH have high cervical HPV prevalence, emphasizing the need for better methods to triage HPV-positive WLWH to differentiate those with clinically important HPV infections (i.e., those that are associated with or will develop into cervical precancer and cancer) versus benign HPV infections destined to clear. Hence several triage biomarkers (e.g., cellular proliferation markers such as p16/Ki67, mRNA transcripts of E6/E7, HPV DNA methylation), and visual approaches such as point-of-care devices/software-enhanced

automated visual evaluation (AVE) have been explored and remain under evaluation for their accuracy to inform optimal management of a positive HPV DNA test result. Randomized trials that evaluate head-to-head comparisons of clinical strategies based on biomarker or visual triage (that may need multiple visits but may require comparatively fewer women to undergo treatment, thereby saving overall resources) versus immediate ablation of all HPV positive WLWH (that may need fewer visits thereby reducing attrition, but result in larger volume of patients undergoing treatment, thereby increasing overall costs) can provide key evidence on optimizing management strategies for screen-positive WLWH. Such trials may also address adaptation of strategies in the context of peri-/post-menopausal involution of the cervical transformation zone, as well as assess the effects of higher rates of cervical inflammation, concurrent presence of sexually transmitted infections, and larger-sized/multifocal precancerous lesions more often seen in WLWH.

Area 3: Facilitating precancer treatment access: In many regions globally, a dearth of well-trained healthcare providers is a key constraint in implementing successful clinical and public health screening programs. In many cervical cancer screening settings in LMICs, 'task shifting' models that rely on nurses and non-physician healthcare providers to replace physician-delivered services have been widely implemented. Yet, in absence of continued training and quality assurance efforts, these efforts remain at risk of losing their intended effectiveness and are difficult to sustain. Several technology-based platforms and adjunctive approaches (e.g., telemedicine, remote monitoring, virtual assistance) for clinical consultations and remote interpretation have been explored and have especially proliferated due to the necessities imposed by the COVID-19 pandemic. Trials to empirically evaluate these approaches may measure outcomes such as increased precancer treatment access rates as well as clinical effectiveness metrics such as post-treatment HPV/ precancer recurrence rates, and rates of appropriate referrals (e.g., proportion of histologically confirmed precancer/cancer detected among women undergoing excisional evaluation). There is a significant 'reverse translation' opportunity from lessons learnt (both from the US to LMICs, and vice versa) while evaluating these strategies.

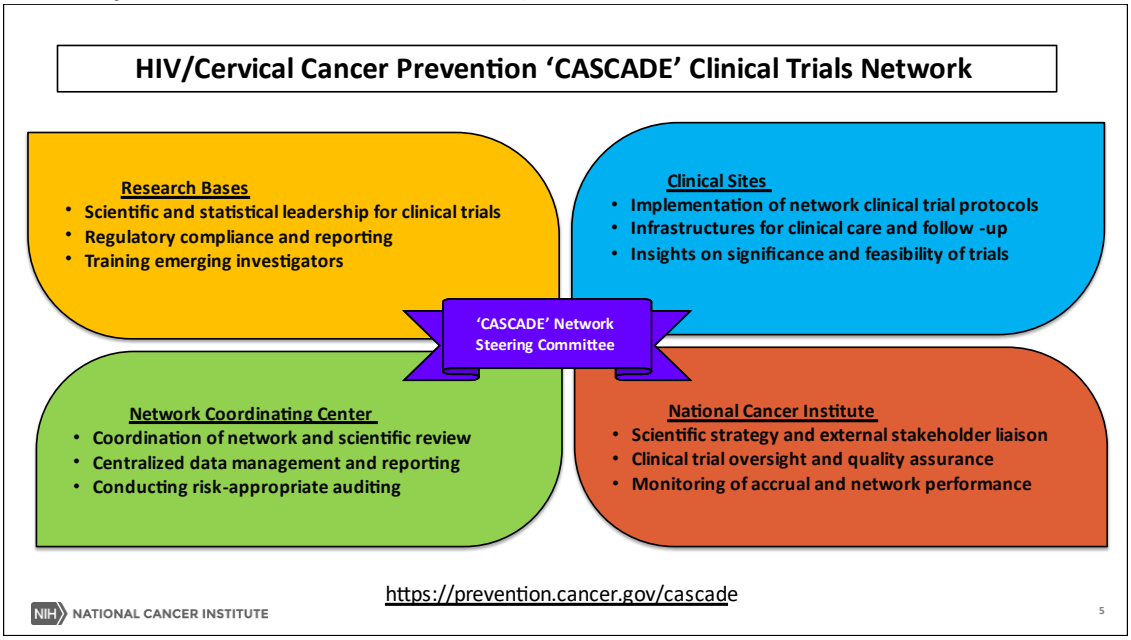
Area 4: Optimizing precancer treatment: Precancer treatment by cryotherapy-based ablation has remained a cornerstone of VIA-based 'screen-and-treat' strategies. Yet, conventional cryotherapy has proven far less amenable for scale up (e.g., due to the recurring costs and inconveniences of freezing gas supplies), and hence several new innovations in ablative treatments have been explored in clinical studies, especially portable/battery-operated thermal ablation devices. Yet, there are variations in definitions of treatability of lesions, which directly lead to variable performance and therefore affect the risk of precancer recurrence. Additionally, the multifocal nature of anogenital disease and the relative immunosuppressive state in WLWH affects post-treatment recurrences. Evaluation of strategies comparing variations in treatment algorithms by type of treatment devices (e.g., portable ablative vs. portable excisional devices) as well as treatability action thresholds by cervical squamocolumnar junction involution status (e.g., transformation zone type 1/2/3) might provide key evidence for optimized implementation for preventive therapy interventions among WLWH. Finally, several novel non-surgical approaches such as HPV therapeutic vaccines and topical HPV therapeutics are under evaluation in early phase clinical trials; and although these may not be readily available for real-world clinical evaluations in the very near-term (pending licensure clinical trials), the ‘CASCADE’ Network may provide an appropriate setting for such evaluations in the future.

III. CASCADE Network Structure and Organizational Units

a. CASCADE Network Organizational Units

The 'CASCADE' network is composed of three types of organizational units working collaboratively and in partnership with the NCI to design and conduct pragmatic clinical trials with hybrid effectiveness-implementation designs, both in resource-constrained settings in low- and middle-income countries (LMICs) as well as in areas of healthcare disparities within the United States.

- One U24 CASCADE Network Coordinating Center (CNCC) *(funded via RFA-CA-21-045 in 2022)*
- Three UG1 Research Bases (RB) *(funded via RFA-CA-21-046 in 2022)*
- Nine UG1 Clinical Sites (CS) *(three sites funded via RFA-CA-21-047 in 2022; six additional sites to be funded via RFA-CA-22-051 in 2023)*



The 'CASCADE' Network involves collaborative development and implementation of clinical trial protocols, with shared decision making through the Network Steering Committee and complementary responsibilities in all steps from trial conceptualization to conduct.

- Research Base investigators propose concepts that are reviewed by the 'CASCADE' Network Steering Committee for feasibility and recommendations for participation by individual Clinical Sites.
- Protocol Teams composed of Research Base and Clinical Site investigators then collaboratively design the clinical trial protocols that require approval by the Network Steering Committee and an NCI Clinical Trials Oversight Committee (CTOC).
- Protocols are activated and implemented in participating Clinical Sites after securing setting-specific ethics and regulatory approvals.
- The CASCADE Network Coordinating Center (CNCC) facilitates coordination, scientific review, data management, and independent risk-appropriate auditing of network clinical trials.
- The 'CASCADE' Network Steering Committee includes representation from each of the network organizational units as well as from the NCI.

Following is the listing of the 'CASCADE' Network Principal Investigators and their institutions:

Organizational Unit	***Principal Investigator(s)/Leads***	***Institution(s)***	***Grant No.***

CASCADE Network Coordinating Center (CNCC)	Suzanne Siminski, MS, MBA, and KyungMann Kim, PhD	Frontier Science, with University of Wisconsin-Madison	U24CA275417
Research Base 1 (RB1)	Rachel Winer, PhD, MPH and Elizabeth Brown, ScD, MS	University of Washington, with Fred Hutchinson Cancer Research Center	UG1CA275402
Research Base 2 (RB2)	Timothy Wilkin, MD, MPH, Anna Giuliano, PhD, and Carla Chibwesha, MD, MSc	Weill Medical College of Cornell Univ., with Moffitt Cancer Center and Univ. of North Carolina at Chapel Hill	UG1CA275414
Research Base 3 (RB3)	Jennifer Smith, PhD, MPH, Michael Hudgens, PhD, and Lameck Chinula, MD, MPH	University of North Carolina at Chapel Hill	UG1CA275403
Clinical Trials Site 1 (CS1): Uganda	Betty Mwesigwa, MBChB, MSc	Makerere University Walter Reed Project, with US Military HIV Research Program and Uganda Cancer Institute	UG1CA275412
Clinical Trials Site 2 (CS2): Kenya	Michael Chung, MD, PhD, MPH and Samah Sakr, MBChB	Emory University, with Coptic Hope Center for Infectious Diseases and Kenyatta National Hospital	UG1CA275400
Clinical Trials Site 3 (CS3): Botswana	Scott Dryden-Peterson, MD, MS and Doreen Ramogola-Masire, MBBS, PhD, MPH	Brigham and Women's Hospital, with Botswana Harvard AIDS Institute Partnership	UG1CA275416

[See: https://prevention.cancer.gov/major-programs/hiv-cervical-cancer-prevention-cascade-clinical-trials-network/organizational-units]

b. CASCADE Network Steering Committee

The CASCADE Network Steering Committee will act as the governing body of the CASCADE Network and seek to integrate the efforts of all Network awardees and the NCI and permit collaborative interactions with the NCI as well as provide joint oversight of Network activities. The committee will include representation from each of the network organizational units and the NCI. Each CASCADE Network grantee (i.e., UG1 Research Bases, UG1 Clinical Sites, and U24 Coordinating Center) and the NCI will have one voting and one non-voting member, as well as other non-voting regular attendees. NCI will be represented by the CASCADE Network Director/NCI Project Scientist (voting member) and the NCI Program Official (non-voting member) and other NCI staff as non-voting regular attendees. The Steering Committee will be chaired on a rotating annual basis by one of the CASCADE grantees.

The primary responsibilities of the Steering Committee include:

- Meeting quarterly and on an additional ad hoc basis, as necessary.
- Approving the standard operating policies (SOPs) for the implementation of network studies.
- Reviewing and prioritizing clinical trial concepts and making recommendations about selection of study implementation sites after balancing competing considerations around scientific focus, geographic distribution of studies across the network, trial accrual targets, protocol implementation complexity, and strategic partnership opportunities.
- Facilitating the process of joint development of appropriate pragmatic clinical trial protocols

by Network awardees and the NCI.

- Other programmatic responsibilities to be addressed jointly, as needed, by Network awardees and the NCI staff.
- Subcommittees: The Steering Committee may establish subcommittees and/or working groups for specific purposes (e.g., to address scientific and administrative issues and/or to coordinate policies, harmonize protocols, implement best practices for research study and clinical trials conduct across sites and participating countries, coordinate regulatory approvals, and for facilitating joint activities).

Role	Unit	Responsibilities
Protocol Chair(s)/Vice Chair(s)	Research Base	Scientific leadership
Protocol Statistician(s)	Research Base	Statistical leadership
Site Principal Investigator(s)	Each participating Clinical Site(s)	On-site clinical and operational leadership
Coordinating Center Data Manager	Coordinating Center	Central data management support
Coordinating Center Statistician *(as applicable)*	Coordinating Center	Statistical support
NCI Project Scientists	NCI	Strategic advice and external stakeholder liaison
Protocol Co-investigator(s)	Research Bases	Specific scientific and operational expertise
Protocol Co-investigator(s)	Clinical Sites	Specific scientific and operational expertise

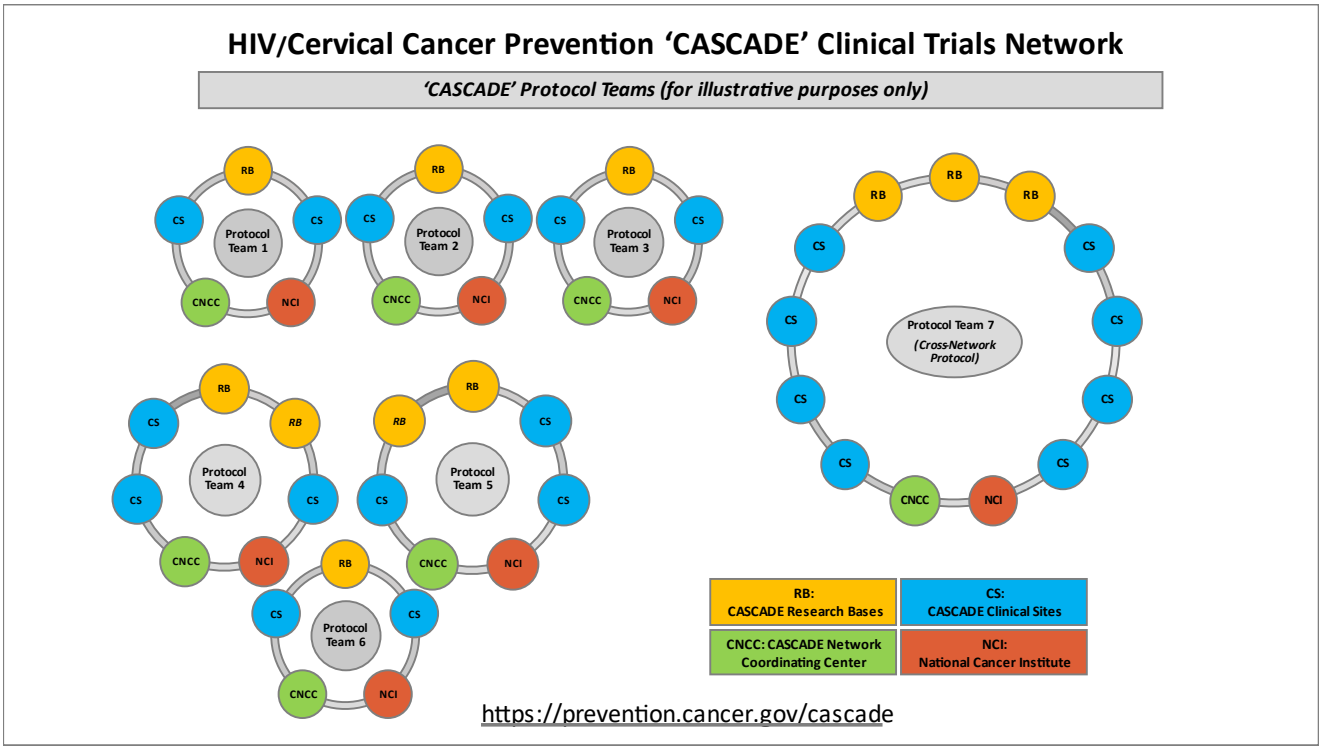
The structure, functions, and responsibilities of the Network Steering Committee will be described in a Steering Committee Charter.

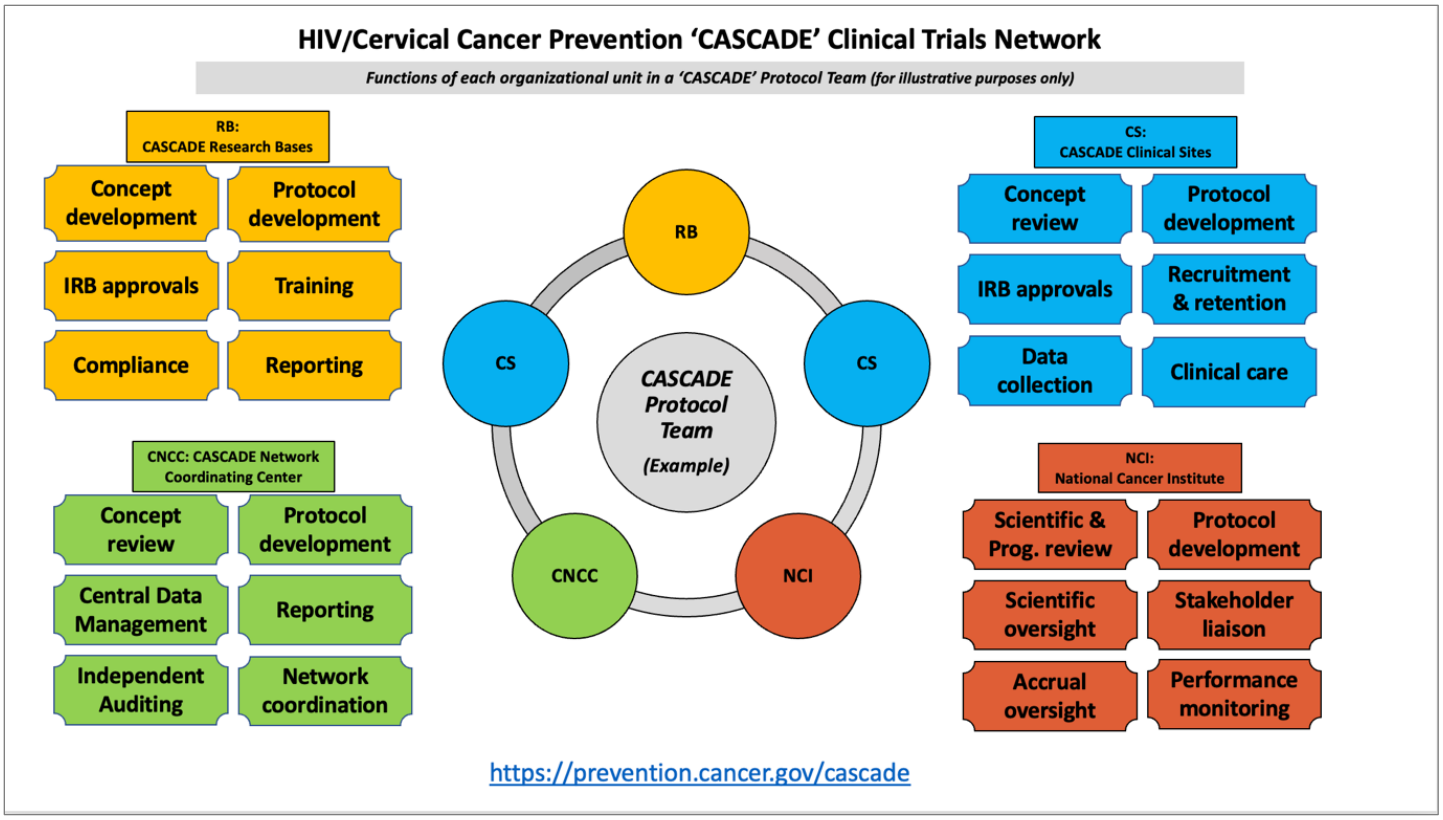
c. CASCADE Protocol Teams

CASCADE Protocol Teams will be the functional units of the CASCADE Network and will be composed of cross-network multidisciplinary groups that work collaboratively to develop and conduct CASCADE clinical trials. At a practice/implementation level the protocol team structure provides a hands-on, decentralized, and equitable working model that actively promotes complementary responsibilities in all steps from trial conceptualization and conduct to completion and dissemination. Each Protocol Team will have leadership and key staff support roles as follows:

Role	Unit	Responsibilities
Protocol Manager	Research Base	Protocol Team's point person for administrative and operational management issues

Protocol Staff	Research Bases	Perform specific protocol tasks (coordination, monitoring, compliance/reporting, etc.)
Protocol Staff	Clinical Sites	Perform specific protocol tasks (local data management, coordination, monitoring, reporting, etc.)
Coordinating Center Staff	Coordinating Center	Central data management support and reporting tasks





d. CASCADE Working Groups

Working Groups in CASCADE are meant to permit network-wide participation (i.e., without the silos of the individual UG1/U24 awards) and address key thematic issues that need network-wide cooperation. While the protocol team structure will permit close bi-/multi-directional inputs and participation of all stakeholders on individual protocols, the working groups will permit identification of complex problems that need coordinated solutions with extensive but rapid input of key stakeholders. Working groups in the network (listed below) have the goal of full and active participation from all participating organizational units and will be co-led by personnel representing the Research Bases, Clinical Sites, and the Coordinating Center.

- *Pragmatic Clinical Trials Methodology Working Group*: charged with the goal of advancing methodologies and designs of pragmatic clinical trials on cervical cancer prevention and control by interfacing with related groups, promoting collaborative methodology-focused publications, and developing a standing scientific meetings/webinar series for the network.
- *Clinical Training/Education Working Group*: charged with the goals of reviewing current standards of clinical care and laboratory practices and workflows (virology, pathology) and recommending need for standardization/quality assurance, expanding opportunities for clinical capacity including remote/on site clinical mentoring to enhance site staff expertise to support CASCADE network protocols.
- *Data Harmonization Working Group*: charged with the goals of optimizing cross-study analyses and comparisons by recommending and implementing strategies to simplify the collection, transfer, harmonization, and analysis of multi-site data sets in support of the CASCADE network studies.

Each working group will have formal agendas and formal meeting minutes that will be distributed via email and posted on the CASCADE Network Coordinating Center gateway portal. In addition,

with the recommendation of the Steering Committee, specific task groups may be added to the network for accomplishing network-wide short-term or longer-term goals.

- The Steering Committee has recommended the creation of an Equity, Diversity, and Inclusion Task Group (EDITAG) which will acknowledge shared goals of equity and inclusion, within an anti-racism and decolonization framework, and serve as a resource group to review and identify areas of improvements in the network on these foundational values.

IV. NIH Role in the 'CASCADE' Cooperative Agreement Program

The administrative and funding instrument used by NIH/NCI for this program is the Cooperative Agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the grant recipients 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 for the project as a whole resides with the recipients, although specific tasks and activities may be shared among the recipients and the NIH.

Specific responsibilities of the CASCADE award's Principal Investigators (PIs) are described in the Funding Opportunity Announcements (FOAs) (RFA-CA-21-045, RFA-CA-21-046 , RFA-CA-21-047, and RFA-CA-22-051). NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

An NCI Program staff member acting as a Project Scientist will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below. Additional NCI staff members may be designated to have substantial involvement (as Project Scientists). Additionally, an agency program official or NIH institute/center (IC) program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice.

The main responsibilities of substantially involved NCI staff members include, but are not limited to, the following activities:

- Working with network recipients to collaboratively manage scientific, administrative, and implementation issues associated in the conduct of clinical trials.
- Ensuring that plans for clinical trial development and conduct, network coordination, scientific review, data management, data reporting, and risk-appropriate auditing of clinical trials are within the scope of the network as well as relevant to the state-of-the-science, NIH/NCI priorities, resources, and availability of funding.
- Reviewing and monitoring accrual and overall progress and performance of clinical trials and key components of the network and implementing any mid-course corrections.
- Serving as a resource for best practices for data management, data reporting, and clinical trials auditing.
- Sponsoring strategy sessions, when indicated, to discuss specific research concepts and network improvement initiatives.
- Overseeing and participating as necessary in clinical trials auditing and quality assurance site visits (on-site and remote) and reviewing auditing reports.
- Informing network recipients about scientific opportunities resulting from NCI-supported programs

and facilitating collaborations with other NCI/NIH-sponsored programs and external initiatives.

- Facilitating formal aspects of collaborations with external organizations including review of any memoranda of understanding and data/material transfer agreements for compliance with NIH/NCI and Federal policies.
- Reviewing data collected and/or generated under this Cooperative Agreement.
- Overseeing data and safety monitoring plans for the proposed Clinical Trials, and final review and approval of requests for use of any biospecimens collected per the approved protocol for Clinical Trials.
- Reviewing compliance with applicable HHS, FDA, OHRP, NIH, and NCI regulations for clinical research involving human research subjects.
- Final review and approval of requests for use of any resources (including data and biospecimens) collected per the approved protocol for network trials. The NCI will have access to all raw data (including imaging data) from clinical trial participants collected and/or generated under this Cooperative Agreement and may periodically review the data. The NCI may also review all records related to recipients' performance under the award for appropriate collection, review, and distribution of biospecimens collected in association with trials.

NCI DCP Staff Members on the 'CASCADE' Network include:

Role	*Name*	*Institutional Title in NCI DCP*
NCI DCP CASCADE Team		
CASCADE Network Director/ NCI Project Scientist	Vikrant Sahasrabuddhe, MBBS, MPH, DrPH	Deputy Chief and Program Director, Breast and Gynecologic Cancer Research Group
NCI Program Official	Silvina Frech, PhD, MS	Program Director, Breast and Gynecologic Cancer Research Group
Nurse Consultant	Margaret House, BSN, RN	Deputy Chief and Nurse Consultant, Prostate and Urologic Cancer Research Group
Program Manager	Emma Brofsky, MSPH	Scientific Program Analyst, Breast and Gynecologic Cancer Research Group
Advisors and Support Staff to NCI DCP CASCADE team		
Strategic and programmatic advisor	Brandy Heckman-Stoddard, PhD, MPH	Chief, Breast and Gynecologic Cancer Research Group
Nurse Consultant	Eileen Dimond, RN, MS	Nurse Consultant, Breast and Gynecologic Cancer Research Group
Program Assistant	Mela Asefa	Staff Assistant, Breast and Gynecologic Cancer Research Group

NCI 'CASCADE' Clinical Trials Oversight Committee (CTOC):

The NCI Project Scientist will organize and chair an NCI CTOC for the 'CASCADE' Network, composed of representatives from relevant NCI Divisions, Offices, and Centers with appropriate expertise. This Committee will be responsible for final protocol approval before the initiation of individual clinical trials. In addition, the Committee will provide recommendations to the NCI Project Scientist(s) and the Steering Committee regarding oversight for these trials, coordination with other relevant NCI-funded initiatives, and other strategic aspects.

The NCI CTOC may recommend suspension, termination, or curtailing of 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 CTOC may also recommend other corrective actions in case of sub-optimal performance of the recipients and/or their affiliated institutions (including recommendations to restructure sub-contractual arrangements). The NCI reserves the right to reduce the budget or withhold an award in the event of substantial recipient underperformance or other substantial failures to comply with the terms of the award.

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 Research Bases/Clinical Sites (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 Research Bases and the Clinical Sites serve as the Study Sponsors and are responsible for managing the day-to-day operations of grant-supported activities using their established policies consistent with NIH requirements for conducting human subject research studies. As indicated in the Notice of Award's Term and Conditions, the Research Bases and the Clinical Sites are responsible for maintaining appropriate certifications of IRB approvals on file.

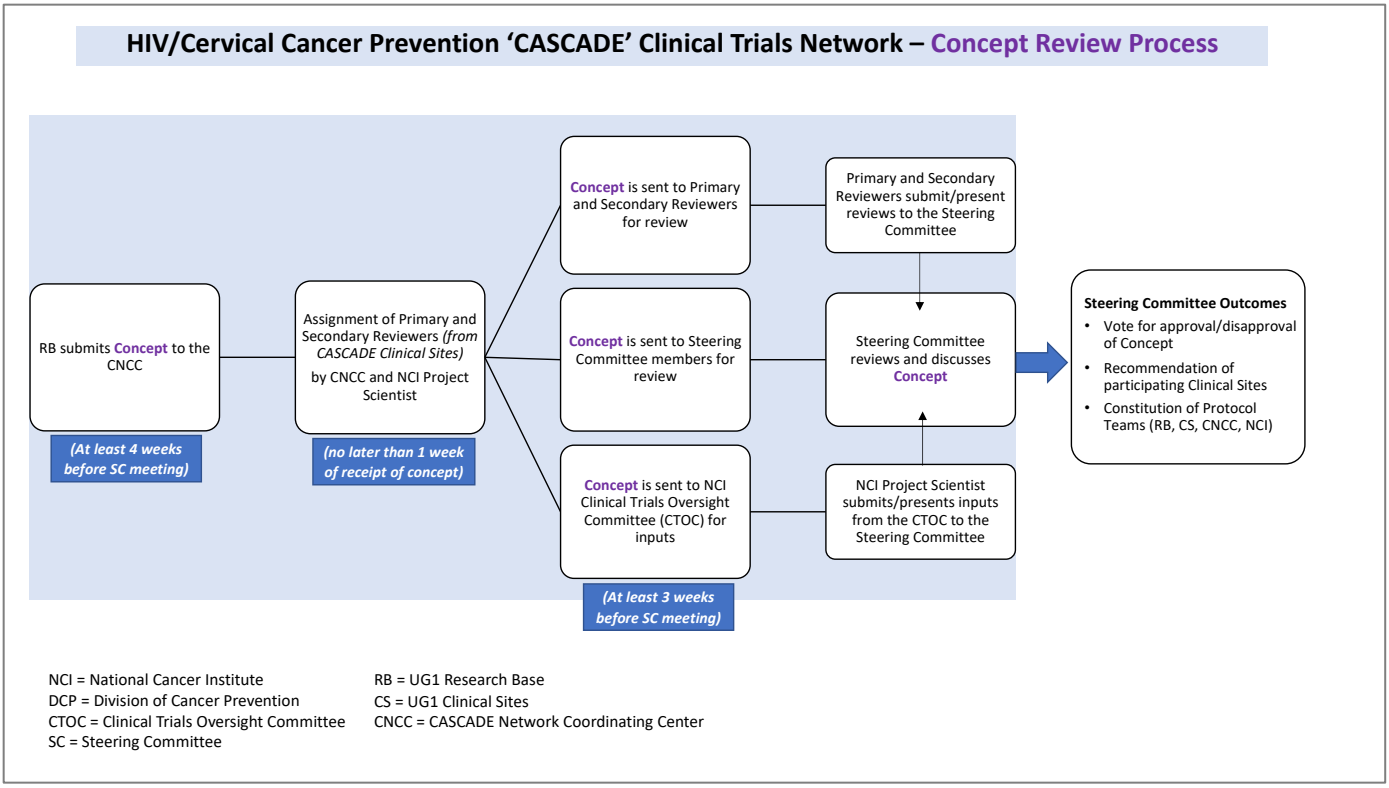
V. Review and Approval Procedures for CASCADE Clinical Trials

The following sections provide broad outlines of the review and approval process for CASCADE clinical trials. Additional details will be described in CASCADE Network Manual of Standard Operating Procedures (M-SOP) to be developed by the CNCC that will be reviewed and approved by the CASCADE Network Steering Committee. Relevant documents will be available on the NCI DCP CASCADE Program website at https://prevention.cancer.gov/cascade and the CASCADE Website/Portal Gateway that will be developed and maintained by the CNCC. In collaboration with the CASCADE Steering Committee and the CASCADE Network Director, the CNCC will be developing an appropriate scoring system framework for review of clinical trial concepts by the Primary and Secondary Reviewers and for voting on approval/disapproval by the Steering Committee.

a. Concepts Review and Approval Process

- At least 4 weeks before the scheduled Steering Committee meeting, the Research Base will submit a Concept to the CNCC.
- No later than 1 week of receipt of the concept, the CNCC will work with the CASCADE Network Director/NCI Project Scientist to identify and assign Primary and Secondary Concept Reviewers.
  Note: Reviewers will be chosen from among investigators from the UG1 Clinical Sites for maximizing the possibilities of receiving direct insights and input on the potential clinical significance and study feasibility-- as was explicitly stated in the funding opportunities announcements. Representatives on the Steering Committee from Clinical Sites that are not chosen as reviewers will also receive the Concepts and may participate in the discussion during the meeting.
- At least 3 weeks before the scheduled Steering Committee meeting, the CNCC will:
  - Send the Concept document and the Concept Review Template to the Primary and Secondary Reviewers.
  - Send the Concept document to the Steering Committee membership for review.
  - Send the Concept document to the NCI Project Scientists for inputs from the NCI CTOC.

- At the scheduled Steering Committee meeting:
  - Primary and Secondary Reviewers will submit/present their Concept reviews to the Steering Committee, and may include important insights into study feasibility, relevance to local and global clinical and operational realities, and reflecting vital perspectives from patients and potential study participants, including women living with HIV, women with personal experience with cervical cancer, and those affected by and having contact with the local healthcare systems.
  - NCI Project Scientists will submit/present inputs from the CTOC on the Concept to the Steering Committee to inform NCI's initial scientific and programmatic feedback on the concept and provide any strategic assessment and any overarching concerns.
  - The Steering Committee members will participate in discussion about the Concept followed by a vote of the Steering Committee for the following outcomes:
    - Approval
    - Disapproval
    - Revise and resubmit
  - All voting members will participate in the open, non-confidential voting, regardless of their role in origination of the concept or their interest in participating in the protocol (i.e., there will no necessity for recusals).
  - The voting decision of approval will be taken by a simple majority of votes casted.
  - The Steering Committee will discuss and provide recommendations on the UG1 Clinical Sites who will be willing to participate as sites on the approved concept. These recommendations will balance competing considerations around scientific focus, geographic distribution of studies across the network, trial accrual targets, protocol implementation complexity, and strategic partnership opportunities.
  - For approved protocols, the Protocol Team will be constituted and charged with development of the study protocol. (For composition of the Protocol Teams, please see Section III.c above)

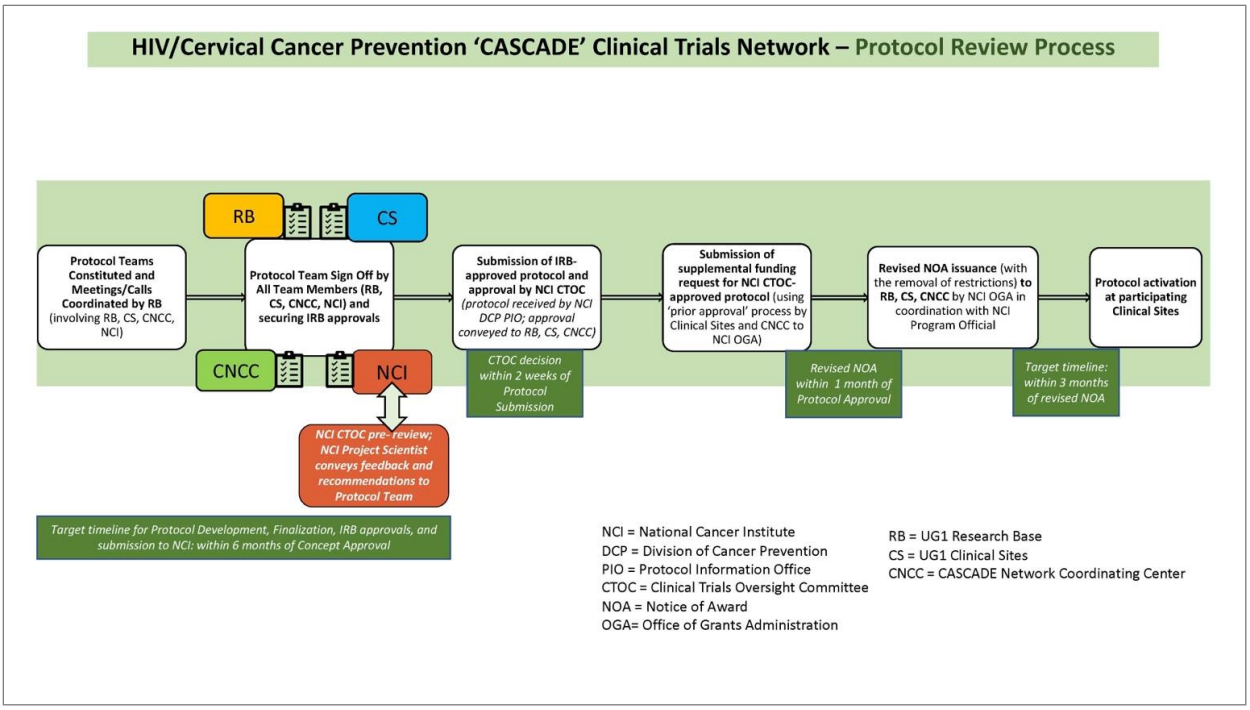


b. Protocol Development and Approval Process

These guidelines outline the process from protocol submission through site activation taking into consideration the necessary scientific, regulatory, and grant award requirements.

- After the Concept approval by the Steering Committee, the Research Bases will lead protocol development by convening regular meetings of the protocol teams with partners from the Clinical Sites, CNCC and the NCI.
- Individual Research Bases may approach protocol development steps differently but are expected to incorporate inputs and reviews from all Protocol Team members, especially incorporating Clinical Site perspectives around study design and implementation.
- As part of the protocol finalization process, the NCI Project Scientist will convene the CTOC to review the protocol. Recommendations and changes from the CTOC will be communicated to the Protocol Chair at the Research Base and the Site PI at the Clinical Site and should be incorporated before seeking ethics and regulatory approvals.
- The Protocol will require review by institutional review boards (IRBs)/institutional ethics committees (ECs) at the Research Base(s) and the participating Clinical Sites (local and country level approvals).
- After the protocol is approved by all relevant ethics and regulatory committees, it will be submitted by the Protocol Chair at the Research Base to the DCP Protocol Information Office for review by the NCI CTOC. The target timeline for submitting protocols for NCI CTOC review is within 6 months of initial Concept approval by the Steering Committee.
- The NCI Project Scientists will convene the CTOC and final approval decisions will be communicated to the Protocol Chair at the Research Base, Site PIs at the Clinical Site, and the CNCC PI.

- As stated in the Notice of Award (NoA), no human subjects research can start until the protocol has been approved by NCI CTOC. It is the responsibility of the recipient institution to maintain appropriate certifications of IRB approvals (from the Research Base, CNCC and the Clinical Site/s enrolling participants) on file.
- Protocol-specific supplemental and set-aside/restricted funding:
  - After CTOC approval, the CNCC will officially request "prior approval" for the use of protocol-specific implementation funds to the NCI Office of Grants Administration (OGA) and the NCI Program Official. These funds are intended to be used for protocol implementation at the Clinical Sites (through agreements between the CNCC and the Clinical Sites) and may not be expended until NCI OGA approves the request and issues a revised Notice of Award (NoA) to the recipient of the U24 CNCC award.



  - In addition to those funds mentioned above, the Clinical Sites will officially request "prior approval" to the NCI OGA and the NCI Program Official for the use of "set aside funds" as indicated in the NoA. These funds included in the "Other Costs" budget line are restricted to cover the costs as described in RFA-CA-21-047 and RFA-CA-22-051 and may not be expended until NCI OGA approves the request and issues a revised NoA to the recipients of the UG1 Clinical Site award.

c. Required Documents and Templates for Concept and Protocol Submission and Review

Templates for Concepts and Protocol Submission and Review will be developed with the CASCADE Network Coordinating Center (CNCC) and will be made available on the NCI DCP CASCADE webpage at https:///prevention.cancer.gov/cascade as well as the 'CASCADE' Website/Portal Gateway Portal that will be developed and maintained by the CNCC. Similarly, the Protocol Submission Worksheet, Protocol Status Update form, and Open-to-Accrual Checklist will be made available on the NCI DCP CASCADE webpage at https://prevention.cancer.gov/cascade

d. Protocol Naming Convention

Protocols associated with a single Research Base will be designated with a "C" prefix, followed by 4 digits as follows:

- The first digit will be reflecting the Research Base Number (1, 2, 3) as follows:
  - 1 = University of Washington-led Research Base
  - 2 = Weill Cornell Medical College-led Research Base
  - 3 = University of North Carolina at Chapel Hill-led Research Base
- The second, third, and fourth digits reflecting the sequential number (e.g., 001, 002, 003, etc.) of the protocols to be proposed by that Research Base.
- Example: "C1001" will be the name for the first protocol from the University of Washington Research Base. "C-3002" will be the name of the second protocol from the University of North Carolina at Chapel Hill.

- Protocols that are not associated with any Research Base or are associated with more than one Research Base will be designated with a "CN" prefix, followed by 3 digits, and designated consecutively upon activation (e.g., "CN001", "CN002", etc.).
- Ancillary protocols will be named with suffixes of "-A", "-B", etc. after the primary number (e.g., "C1001-A" and "CN101-A").

e. Protocol Version Convention

Protocols will start at version 1.0 and any change prior to Final NCI CTOC Approval will result in the protocol being versioned to the next whole number. Each subsequent amendment after Final NCI CTOC will be versioned using .1, .2, .3, etc.

- Example: A protocol at version 3.3 received Final DCP Approval at version 3.0 and has been amended three times since Final DCP Approval (3.1, 3.2, and 3.3).

The protocols should be written with flexibility allowing all sites to follow the protocol according to their local IRB. There is no need for separate protocol names or versions of a protocol by site or country. When a protocol opens under the initial version (e.g., 3.0), all sites will follow that protocol and version. When the protocol is amended (e.g., 3.1), all sites will submit the new version of the protocol to their IRB. Each site will continue to follow the old version of the protocol until they receive approval to the new version. This method will keep the protocol naming and versioning simple as well as easier to explain in publications.

f. Other Submission policies

Details about other submission policies (e.g., amendment, ancillary studies) will be updated in the next version of the program guidelines.

VI. CASCADE Protocol Conduct and Oversight

Details about the following requirements (and others as applicable) will be described in the CASCADE Manual of Standard Operating Procedures (M-SOP) to be developed by the CNCC that will be reviewed and approved by the CASCADE Network Steering Committee.

- Study Specific Monitoring Plans
- Delegation of Tasks Logs (DTL) and NCI Registration and Credential Repository (RCR)
- Monthly Minimum Data Set (MDS)

- Treatment Assignment Codes (TAC) / Treatment Assignment Descriptions (TAD)
- Serious Adverse Events and Protocol Deviations
- NCI/DCP Accrual Quality Improvement Program (AQuIP)
- ClinicalTrials.gov Registration and Result Reporting
- Data and Safety Monitoring Requirements
- Record Retention and Access
- Other related Documents

(Please note this list is only illustrative; some elements may be modified as per CASCADE-specific requirements).

VII. Other Network Policies

Details about the following requirements (and others as applicable) will be described in the CASCADE Manual of Standard Operating Procedures (M-SOP) to be developed by the CASCADE Network Coordinating Center that will be reviewed and approved by the CASCADE Network Steering Committee.

- Policies for developing and amending Network wide Standard Operating Procedures (SOPs)
- Resource/data sharing policies
- Publications Policy (manuscripts, abstracts)
- Policies for media/publicity and branding

VIII. Abbreviations List

ABBREVIATION	FULL TERM
AIDS	Acquired Immune Deficiency Syndrome
AQuIP	Accrual Quality Improvement Program
ART	Antiretroviral Therapy
AVE	Automated Visual Evaluation
CASCADE	HIV/Cervical Cancer Prevention 'CASCADE' Clinical Trials Network
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CNCC	CASCADE Network Coordinating Center
CRO	Contract Research Organization
CS	Clinical Site
CTOC	Clinical Trials Oversight Committee
CTRO	Clinical Trials Reporting Office
CTRP	Clinical Trials Reporting Program
DCP	Division of Cancer Prevention
DTL	Delegation of Task Log
FDA	Food and Drug Administration
FOA	Funding Opportunity Announcement
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

IC	Institute/Center
IRB	Institutional Review Board
LMIC	Low- and Middle-Income Countries
M-SOP	Manual of Standard Operating Procedures
MDS	Monthly Minimum Data Set
mHealth	Mobile Health
MOU	Memoranda of Understanding
NCI	National Cancer Institute
NIH	National Institutes of Health
NoA	Notice of Award
OD	Office of the Director at the NIH
OHRP	Office for Human Research Protections
PEPFAR	US President's Emergency Plan for AIDS Relief
PHS	Public Health Service
PI	Principal Investigator
PIO	Protocol and Information Office
PLWH	People Living with HIV
RB	Research Base
RCR	Registration and Credential Repository
SC	Steering Committee
SOP	Standard Operating Policies
TAC	Treatment Assignment Codes
TAD	Treatment Assignment Descriptions
USAID	US Agency for International Development
VIA	Visual Inspection with Acetic Acid
WHO	World Health Organization
WLWH	Women Living with HIV