

*Pre-Application Webinar for
Funding Opportunity Announcements*

**HIV/Cervical Cancer Prevention
'CASCADE' Clinical Trials Network**

RFA-CA-21-045: U24 Coordinating Center

RFA-CA-21-046: UG1 Research Bases

RFA-CA-21-047: UG1 Clinical Sites

HPV-mediated Cervical Carcinogenesis in the Context of HIV

Higher burden of HPV and cervical cancer among women with HIV

- accentuated by immunosuppression
- refractory to antiretroviral therapy

Cervical cancer among women living with HIV

- younger age at cancer diagnosis
- more aggressive clinical course
- less responsiveness to treatment

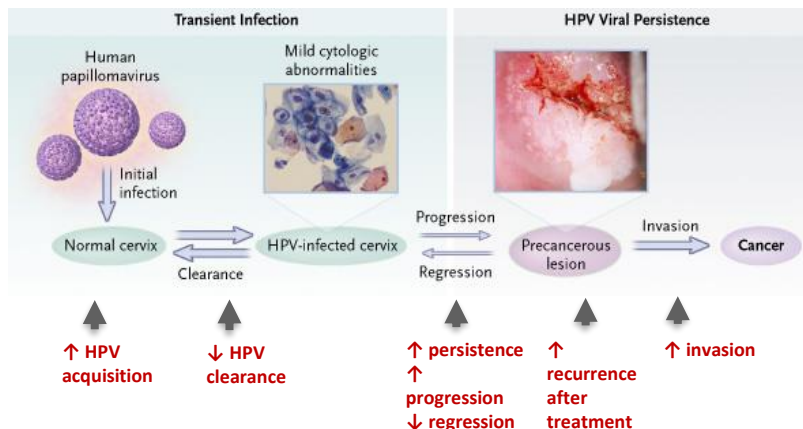
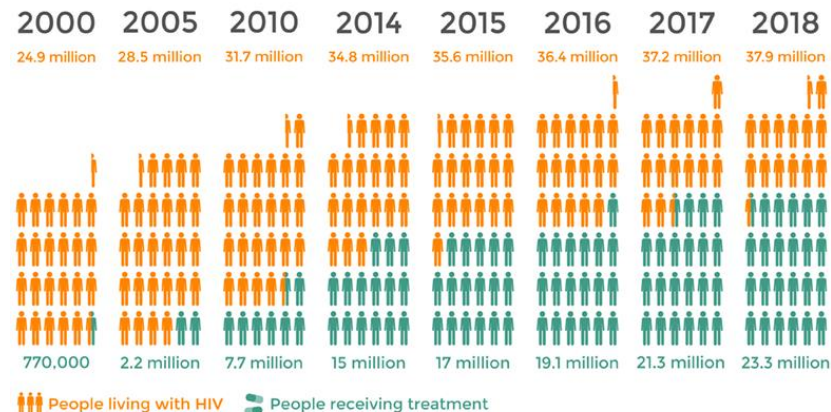


Figure ref: Wright & Schiffman, NEJM 2003

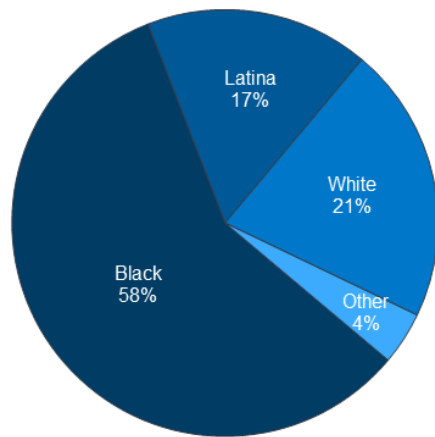


Ref: <https://www.avert.org/global-hiv-and-aids-statistics>

Why Should---and How Could---We Let Women With HIV Die Due to Lack of Effective Cervical Cancer Prevention Services after Extending their Lives with Antiretroviral Therapy?

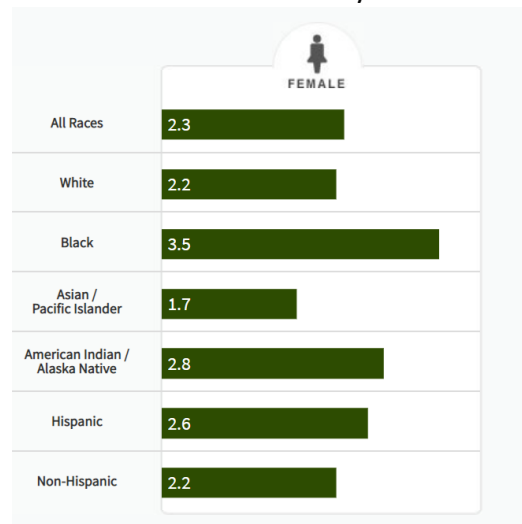
Racial and Ethnic Disparities are a prominent feature influencing the burden of both HIV/AIDS and Cervical Cancer in the United States

HIV/AIDS Diagnoses among Women in the US



Source: Kaiser Family Foundation 2018
<https://www.kff.org/hiv/aids/fact-sheet/women-and-hiv-aids-in-the-united-states>

Cervical Cancer Mortality Rates



Source: NCI SEER Cancer Fact Sheets
<https://seer.cancer.gov/statfacts/html/cervix.html>

Rationale for the 'CASCADE' Clinical Trials Network

- Acceleration in key catalytic technologies and regulatory pathways:
 - HPV self-sampling approvals ('Last Mile' Initiative)
 - Development of point-of-care visual/diagnostic approaches
 - Multiple portable ablative/excisional devices in late-trials



- Renewed impetus on bilateral and multilateral initiatives for cervical cancer screening and treatment:
 - PEPFAR 'Go Further' HIV-Cervical Cancer Partnership expansion
 - World Health Organization's Global Cervical Cancer Elimination Initiative



The proposed 'CASCADE' Network will seek to conduct **pragmatic clinical trials evaluating the effectiveness of clinically-proven interventions in intended-use settings** with a goal to optimize the cervical cancer screening and treatment cascade for women living with HIV

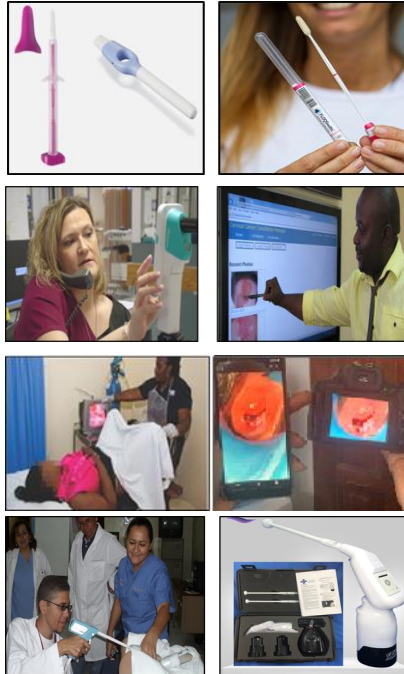
'CASCADE' Clinical Trials Network: Focus Areas and Study Designs

Clinical Trial Focus Areas

- Increasing Screening Uptake
- Improving Management of Screen Positives
- Facilitating Precancer Treatment Access
- Optimizing Precancer Treatment

Sites of Clinical Trials

- Resource constrained settings in **Low- and Middle-Income Countries (LMICs)**
- Settings with high disease-burden and health disparities within the **United States**



Pragmatic Phase 3/Phase 4 Clinical Trials with 'Hybrid' Effectiveness-Implementation Designs

- *Clinical effectiveness outcomes*
 - Rates of HPV detection/precancer detection
 - Rates of post-treatment HPV/precancer recurrence
 - Rates of appropriate referrals
- *Information to inform future implementation and scale-up*
 - Rates of uptake of intervention and reductions in attrition rates
 - Costs, acceptability, and implementation fidelity

'CASCADE' Clinical Trials Network: Potential Areas of Focus and Clinical Trial Designs

Increasing Screening Uptake



Compare HPV self-sampling strategies vs. standard of care:

- **Linked to HIV clinic visits**
- **Targeted outreach (navigators/mHealth)**
- **Camp-based approach**
- **Door-to-door coverage**

Outcomes

- **Difference in cervical precancer detection rates and screening uptake rates**
- **Costs, acceptability, HIV-related stigma**
- **System-level barriers and facilitators**

'CASCADE' Clinical Trials Network: Potential Areas of Focus and Clinical Trial Designs

Improving Management of Screen Positives



Compare management strategies:

- Same-visit ablation of HPV positives (except visible cancers) without intermediate biopsy *versus* triage with molecular biomarkers or visual approaches (same vs. deferred-visit)
- Adaptation of strategies in relation to peri-/post-menopausal involution of the cervical transformation zone, higher cervical inflammation, concurrent presence of sexually transmitted infections, and larger-sized/multifocal precancerous lesions more often seen in WLWH.

Outcomes

- Post-treatment HPV/ precancer recurrence rates
- Reduction in attrition through cascade
- Harms/risks of treatment
- Costs and acceptability

'CASCADE' Clinical Trials Network: Potential Areas of Focus and Clinical Trial Designs

Facilitating precancer treatment access



Compare clinical decision-making strategies:

- Independent decision-making by primary providers ('Task shifting')
- Telemedicine-based specialist consultations

Outcomes

- Post-treatment HPV/ precancer recurrence rates
- Rates of appropriate (i.e., precancer/cancer) referrals

'CASCADE' Clinical Trials Network: Potential Areas of Focus and Clinical Trial Designs

Optimizing precancer treatment



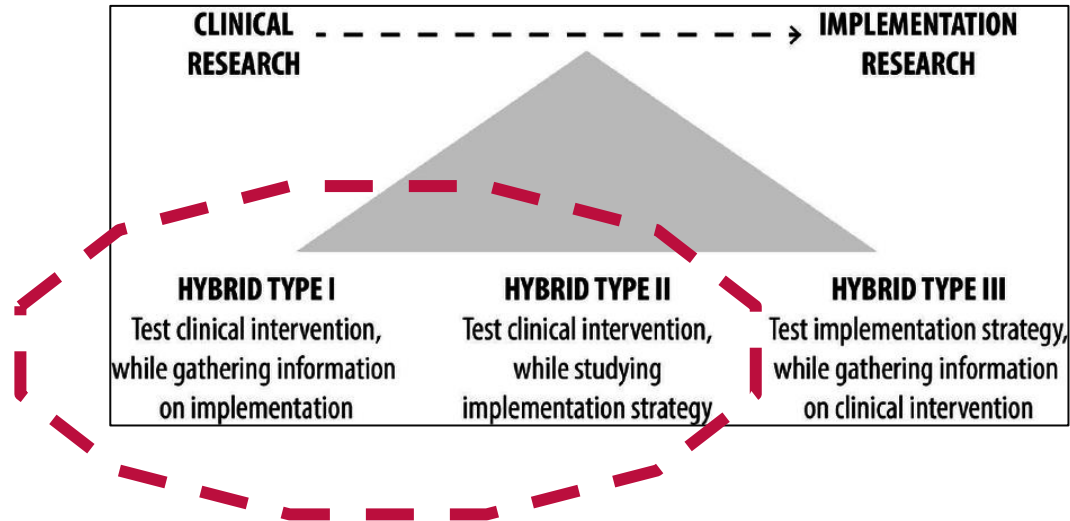
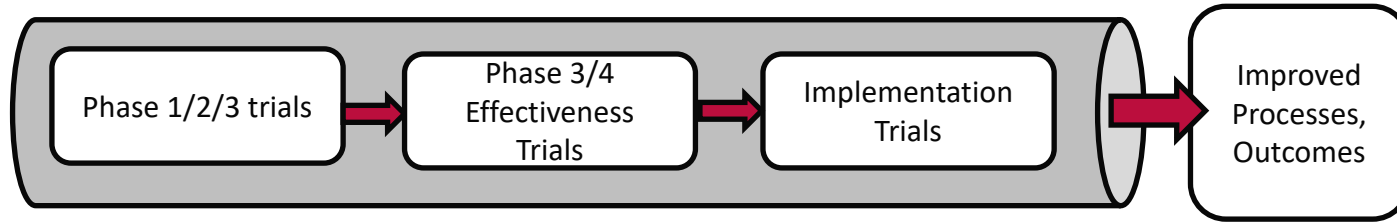
Compare 'screen-and-treat' strategies with variations in:

- Portable devices (ablation, excision)
- Treatability thresholds by cervical squamocolumnar junction involution status

Outcomes

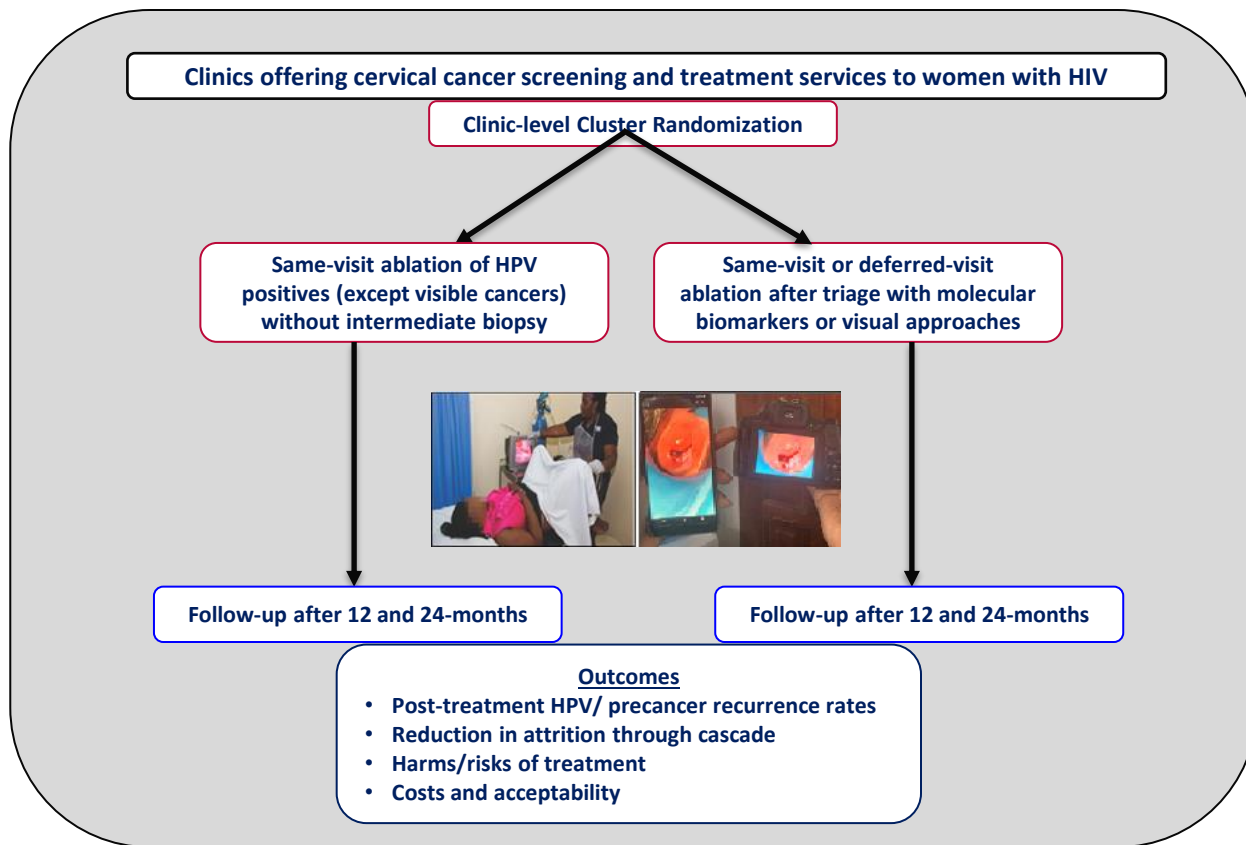
- Post-treatment HPV/ precancer recurrence rates
- Costs, acceptability
- Reduction in attrition through cascade

'CASCADE' Clinical Trials Network: Designs of Clinical Trials




Ref: Conceptual Framework from Curran et al. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care* 2012;50:217-26.

'CASCADE' Clinical Trials Network: design outline of a potential clinical trial



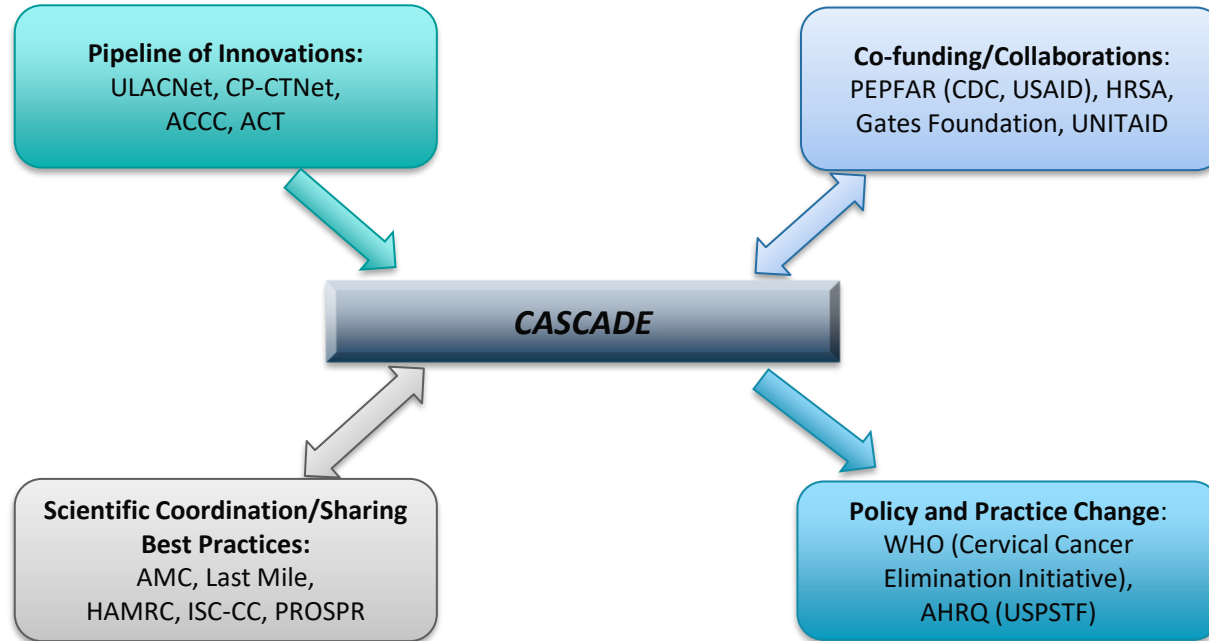
The 'CASCADE' Clinical Trials Network will seek to fill a gap in the spectrum of NCI-supported clinical and translational research on cervical cancer prevention

<div>Blue: not exclusively HIV focused</div> <div>Red: primarily HIV-focused</div>	T0 & T1	T2	T2	T3 & T4
	Pre-Clinical Development	Phase 1/2/3 Clinical Trials	Phase 3/Phase 4 Clinical Trials	Dissemination & Implementation
	Translation to Humans	Translation to Patients		Translation to Practice
				
Licensed HPV vaccines: dosing/uptake		CP-CTNet, ULACNet	HPV-1DT	ISC3
Novel HPV vaccines	PREVENT	CP-CTNet		
Licensed HPV tests: self-sampling			Last Mile, CASCADE	PROSPR
Novel HPV molecular biomarkers	EDRN, ACT	ACCC, ACT, ULACNet	CASCADE	
Novel precancer diagnostic & imaging	EDRN, ACT	ACCC, ACT	CASCADE	
Novel ablative/excisional treatments		ACT	CASCADE	
HPV therapeutic vaccines	PREVENT	CP-CTNet, ULACNet, AMC		
Topical precancer therapeutics	PREVENT	CP-CTNet, ULACNet, AMC		
Management of invasive cancers		NCTN, NCORP, AMC	NCTN, NCORP, AMC	

ACCC: Cancer Moonshot 'Accelerating Cervical Cancer Control' initiative
 ACT: Affordable Cancer Technologies Program
 AMC: AIDS Malignancy Consortium
 CP-CTNet: Cancer Prevention Clinical Trials Network
 EDRN: Early Detection Research Network
 HPV-1DT: NCI HPV vaccine One vs. Two dose trial in Costa Rica
 ISC3: Implementation Science Centers for Cancer Control

Last Mile: NCI Cervical Cancer 'Last Mile' Initiative
 NCORP: NCI Community Oncology Research Program
 NCTN: NCI National Clinical Trials Network
 PREVENT: Chemoprevention Agent Preclinical Development Program
 PROSPR: Population-based Research to Optimize the Screening Process
 ULACNet: US Latin American Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network

'CASCADE' Clinical Trials Network: External Organizational Linkages



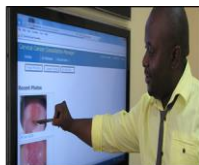
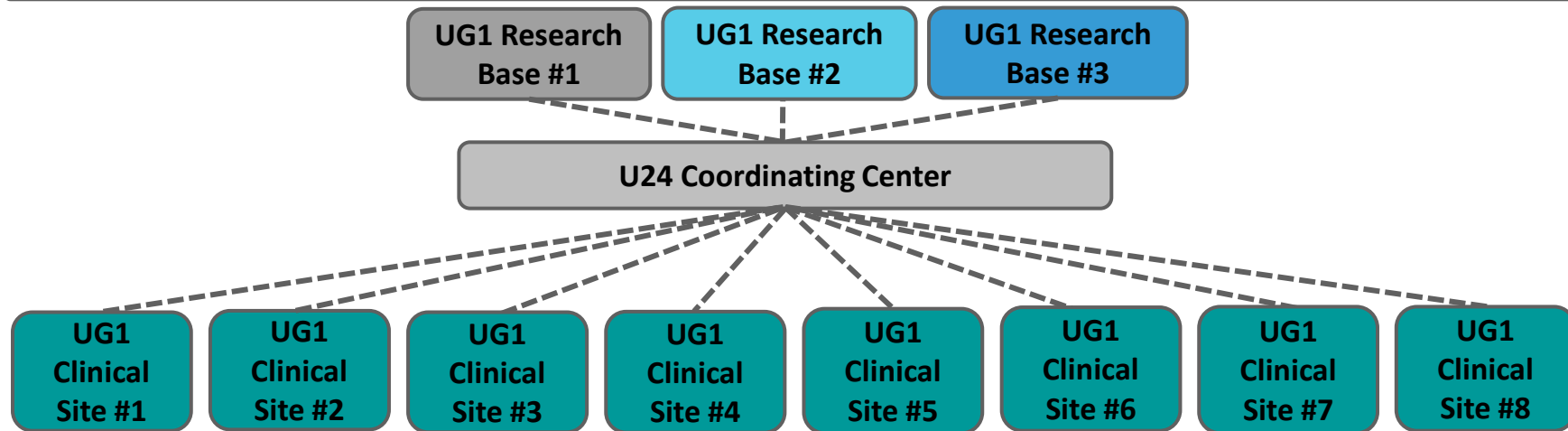
AHRQ: Agency for Healthcare Research and Quality
CDC: Centers for Disease Control and Prevention
HRSA: Health Resources and Services Administration
PEPFAR: President's Emergency Plan for AIDS Relief
USAID: US Agency for International Development
USPSTF: United States Preventive Services Task Force
WHO: World Health Organization

ACCC: Cancer Moonshot 'Accelerating Cervical Cancer Control' initiative
ACT: Affordable Cancer Technologies Program
AMC: AIDS Malignancy Consortium
CP-CTNet: Cancer Prevention Clinical Trials Network
ISC-CC: Implementation Science Centers for Cancer Control
Last Mile: NCI Cervical Cancer 'Last Mile' Initiative

NCTN: NCI National Clinical Trials Network
NCORP: NCI Community Oncology Research Program
HAMRC: HIV-Associated Malignancy Research Centers
PROSPR: Population-based Research to Optimize the Screening Process
ULACNet: US Latin American Caribbean HIV/HPV-Cancer Prevention Clinical Trials Network

HIV/Cervical Cancer Prevention 'CASCADE' Clinical Trials Network

'CASCADE' Network Steering Committee and NCI Oversight Committee



<https://prevention.cancer.gov/cascade>

‘CASCADE’ Network FOAs: Scope of Activities

U24 Coordinating Center: [RFA-CA-21-045](https://www.fda.gov/oc/foia/foia-requests)

Network-wide coordination and scientific review of clinical trial concepts and protocols

- overall network coordination: administrative support, program and logistical coordination.
- scoring system framework for review of clinical trial concepts and protocols
- organize, support, and coordinate activities of a network-wide data safety monitoring committee
- support standardized receipt and bidirectional secure distribution of protocol and review documents

Provision of centralized data management support for network clinical trials

- ‘fit-for-purpose’ centralized clinical data management system (cloud-based and offline, facility and remote/field-based).
- data management policies for quality data collection to ensure adequacy, integrity, and legitimacy of data
- routine and ad-hoc reporting of clinical trials data using pre-designed and custom formats.
- develop appropriate web-services as per industry best practices for system-to-system data exchange of clinical trial data.

Conduct of independent risk-appropriate auditing of network clinical trials

- Independent risk-appropriate auditing activities (remote/virtual and on-site) of UG1 Research Bases and UG1 Clinical Sites, as per GCP and applicable regulatory requirements, federal regulations, and NIH/NCI/DCP policies.
- Collaboratively identifying areas for systemic and policy-level improvements in order to increase both efficiency and compliance, ensure the protection of human subjects, and enhance the quality and integrity of ‘CASCADE’ clinical trials.

‘CASCADE’ Network FOAs: Scope of Activities

UG1 Research Base: [RFA-CA-21-046](#)

- **Provide an established organizational structure, with scientific and statistical leadership** for developing, implementing, and analyzing multi-institutional pragmatic clinical trials in the primary focus areas of the ‘CASCADE’ Network in partnership with the ‘CASCADE’ Network grantees and the NCI.
 - increasing screening uptake
 - improving the management of screen positives
 - facilitating precancer treatment access
 - optimizing precancer treatment for cervical cancer prevention in women with HIV
- **Assume responsibility for study operations**, including efficient protocol development, and compliance with US and international regulatory requirements, human subject protection requirements, and applicable NIH, NCI, and DCP policies.
- **Provide opportunities for expanding training and capacity-building initiatives** for programmatic implementation and scale-up of cervical cancer prevention interventions in intended use settings.

The range of experience and expertise for each UG1 Research Base should encompass ***at least two of the four scientific focus areas*** of the ‘CASCADE’ Network

‘CASCADE’ Network FOAs: Scope of Activities

UG1 Clinical Sites: [RFA-CA-21-047](#)

- **Participate as implementing sites of the multicenter network** of institutions/organizations by providing access to potential study participants **for enrollment in pragmatic clinical trials** in the ‘CASCADE’ Network.
- **Interact with the UG1 Research Bases** by
 - providing insight into clinical significance during concept development,
 - identifying healthcare disparities in their local populations that could be studied,
 - providing input on feasibility during protocol development in the ‘CASCADE’ Network,
 - creating recruitment plans to achieve trial accrual goals.
- **Interact with the U24 Coordinating Center:**
 - for undertaking activities related to centralized data management activities
 - for risk-appropriate clinical trials auditing in support of ‘CASCADE’ clinical trials,

The range of experience and expertise for UG1 Clinical Sites should encompass **at least three of the four scientific focus areas of the network.**

‘CASCADE’ Network FOAs: Scope of Activities

UG1 Clinical Sites: [RFA-CA-21-047](#) (page 2)

- **Domestically in the US:** the UG1 Clinical Sites should include a major focus on women with HIV covered by Medicaid, the CDC National Breast and Cervical Cancer Early Detection Program (NBCCEDP), or by the Health Resources and Services Administration (HRSA)-Ryan White HIV/AIDS Care Program funding, or seen at HRSA-funded Federally Qualified Health Centers (FQHCs) including Community Health Centers, Migrant Health Centers, Health Care for the Homeless, and Health Centers for Residents of Public Housing.
- **Internationally,** the UG1 Clinical Sites should include a major focus on women with HIV receiving clinical care services through ongoing cervical cancer prevention and control initiatives, such as that through the PEPFAR 'Go Further' HIV-Cervical Cancer Partnership in high burden countries in sub-Saharan Africa, the World Health Organization's efforts through the Global Cervical Cancer Elimination Initiative, or other national-funded and/or bilaterally/multilaterally-funded clinical care service delivery initiatives.

'CASCADE' Network FOAs: Network Steering Committee

U24 Coordinating Center: [RFA-CA-21-045](#), **UG1 Research Base:** [RFA-CA-21-046](#), **UG1 Clinical Sites:** [RFA-CA-21-047](#)

Steering Committee:

- Governing body of the 'CASCADE' Network
- Seek to integrate the efforts of all network recipients
- Permit collaborative interactions with the NCI
- Provide joint oversight of network activities.

Composition:

- Two representatives from each network recipient (i.e., from each UG1 Research Bases, each UG1 Clinical Sites, and the U24 Coordinating Center), one of whom must be the PD/PI, who will jointly have one vote for the award they represent.
- NCI Project Scientist(s), who will collectively have one vote for NCI.
- NCI Program Official will be a non-voting member of the Steering Committee.
- Additional non-voting members may be added to the committee as needed.

'CASCADE' Network FOAs: Other Key Application Preparation Guidance

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

Protocol Teams:

- Protocol Chair(s): UG1 Research Bases
- Protocol Statisticians: UG1 Research Bases
- Site Principal Investigator #1: UG1 Clinical Site #1
- Site Principal Investigator #2: UG1 Clinical Site #2
- Site Principal Investigator #3: UG1 Clinical Site #3
- Site Principal Investigator #4: UG1 Clinical Site #4
- ...
- NCI Project Scientist(s)

Research Support:

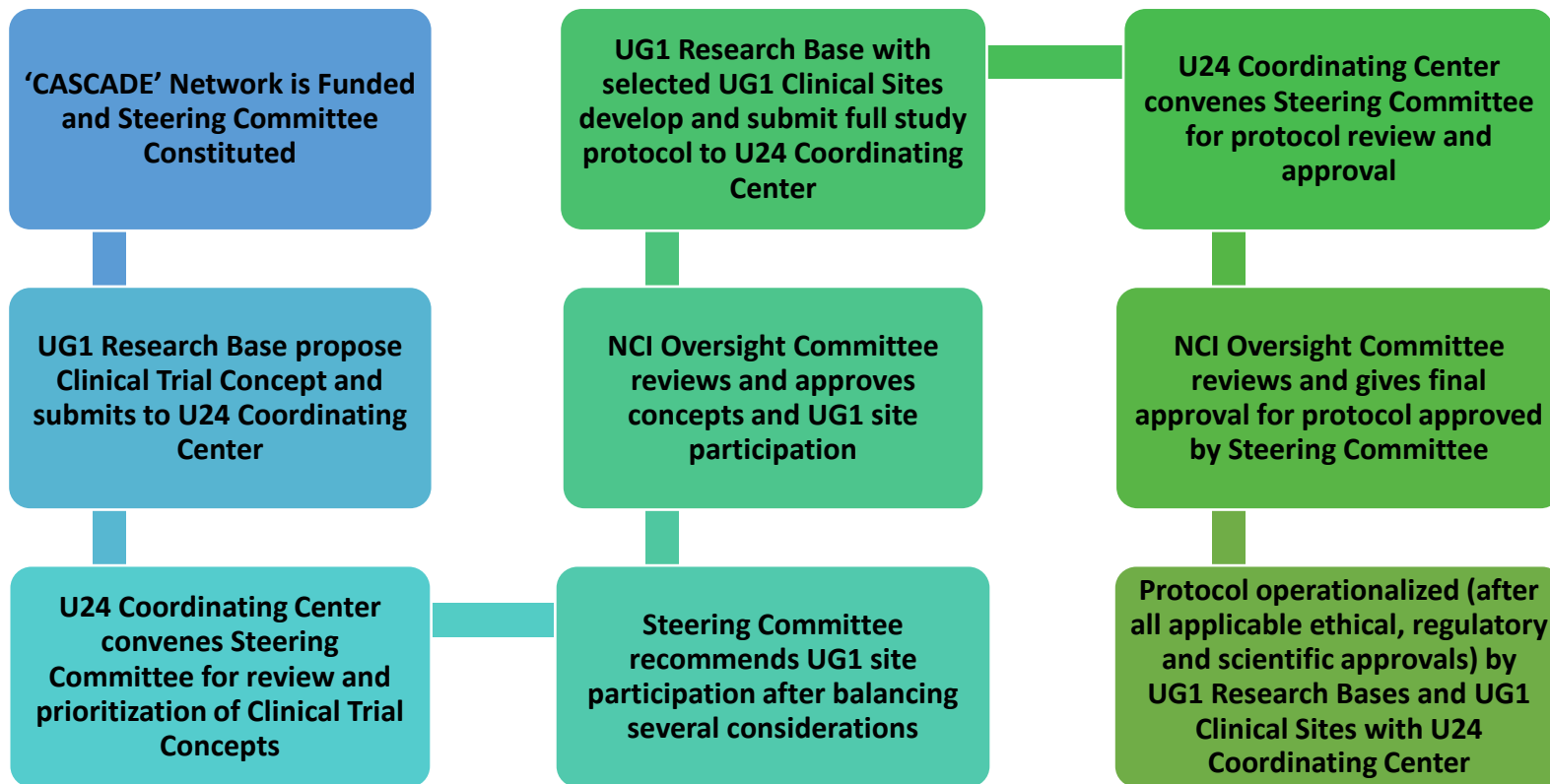
- Oversight, Compliance: UG1 Research Base Admin Staff
- Local Site Clinical Support: UG1 Clinical Site Clinicians
- Local Site Operations Support: UG1 Clinical Site Research Staff
- Data Management Support: U24 Coordinating Center: Unit 2
- Risk-appropriate Auditing: U24 Coordinating Center: Unit 3

Concept and Protocol Review:

- Network Steering Committee
- NCI Oversight Committee
- Coordination/Scientific Review: U24 Coordinating Center: Unit 1

'CASCADE' Network FOAs: Concept and Protocol Development Process

U24 Coordinating Center: [RFA-CA-21-045](#), **UG1 Research Base:** [RFA-CA-21-046](#), **UG1 Clinical Sites:** [RFA-CA-21-047](#)



HIV/Cervical Cancer Prevention 'CASCADE' Clinical Trials Network

'CASCADE' Network Steering Committee and NCI Oversight Committee

UG1 Research
Base #1

UG1 Research
Base #2

UG1 Research
Base #3

U24 Coordinating Center

UG1
Clinical
Site #1

UG1
Clinical
Site #2

UG1
Clinical
Site #3

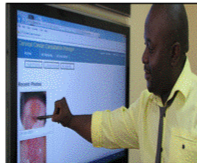
UG1
Clinical
Site #4

UG1
Clinical
Site #5

UG1
Clinical
Site #6

UG1
Clinical
Site #7

UG1
Clinical
Site #8



<https://prevention.cancer.gov/cascade>

‘CASCADE’ Network FOAs

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

‘CASCADE’ Network FOAs: Eligibility

	U24 Coordinating Center	UG1 Research Bases	UG1 Clinical Sites
	RFA-CA-21-045	RFA-CA-21-046	RFA-CA-21-047
Applicants			
US Institutions	Yes	Yes	Yes
Foreign (LMIC) institutions	<i>No</i>	Yes	Yes*
Components			
US Institutions	Yes	Yes	Yes
Foreign (LMIC) institutions	Yes	Yes	Yes*

*Clarified in [NOT-CA-22-009](#)

‘CASCADE’ Network FOAs

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

‘CASCADE’ Network FOAs: Application Submission Information

	U24 Coordinating Center	UG1 Research Bases	UG1 Clinical Sites
	RFA-CA-21-045	RFA-CA-21-046	RFA-CA-21-047
Maximum Direct Costs	\$750,000	\$400,000	\$200,000
Page Limits			
• Specific Aims	1 page	1 page	1 page
• Research Strategy	12 pages	12 pages	6 pages*
Other Attachments			
• No. of attachments	3	1	1
• File names of attachments	‘Coordination Projects’, ‘Data Management Projects’, ‘Auditing Projects’	‘Past Achievements’	‘Catchment Area’

*FOA instructions for page limits supersede instructions on <https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/page-limits.htm#other>

'CASCADE' Network FOAs

U24 Coordinating Center: [RFA-CA-21-045](#), **UG1 Research Base:** [RFA-CA-21-046](#), **UG1 Clinical Sites:** [RFA-CA-21-047](#)

	U24 Coordinating Center	UG1 Research Bases	UG1 Clinical Sites
	RFA-CA-21-045	RFA-CA-21-046	RFA-CA-21-047
Maximum Direct Costs	\$750,000	\$400,000	\$200,000
Research Strategy Page Limits	12 pages	12 pages	6 pages*
• Sub-section A	Coordinating Center Leadership Capabilities	Scientific and Statistical Leadership	Clinical and Research Leadership
• Sub-section B	Developing and Implementing Coordinating Center activities	Developing and Implementing the Scientific Agenda	Implementing Clinical Trials
• Sub-section C	Functional Areas Activities of the Coordinating Center	Study conduct and strategies for recruitment and retention	Strategies for recruitment and retention
• Sub-section D	Milestones and Adaptability	Milestones and Adaptability	--

*FOA instructions for page limits supersede instructions on <https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/page-limits.htm#other>

'CASCADE' Network FOAs: Budget:
U24 Coordinating Center: [RFA-CA-21-045](#)

Maximum Direct Costs: \$750,000 per year for up to 5 years

Key Personnel Costs:

- ***PD/PI Effort Commitment***

- Contact PD/PI: minimum effort: 2.4 person-months (20%).
- Multiple PD/PI: each PD/PI: minimum effort of 1.2 person-months (10%)
- Levels cannot be reduced during the project period.

- ***Functional Unit Director***

- Substantial efforts: e.g., minimum 1.2 person-months (10%).
- Coordinating Center PD/PI can serve in a dual role as Functional Unit Director for one unit; these efforts should be in addition to those expended for PD/PI role

‘CASCADE’ Network FOAs: Budget:
U24 Coordinating Center: [RFA-CA-21-045](#)

Maximum Direct Costs: \$750,000 per year for up to 5 years

Functional Units:

Network Coordination and Scientific Review Unit –

- Personnel/activities for developmental, operational, and scientific review aspects

Data Management and Reporting Unit–

- ‘Fit-for-purpose’ centralized clinical data management system (cloud & offline, clinic- and field-based).
- Data management policies (adequacy, integrity, and legitimacy of data and information).
- Routine and ad-hoc reporting of clinical trials data
- Web-services as per industry best practices for system-to-system data exchange.

Clinical Trials Auditing Unit–

- Independent risk-appropriate auditing activities (remote/virtual and on-site) of UG1 Research Bases and UG1 Clinical Sites, as per GCP and applicable regulatory requirements, federal regulations, and NIH/NCI/DCP policies.

‘CASCADE’ Network FOAs: Budget:
UG1 Research Base: [RFA-CA-21-046](#)

Maximum Direct Costs: \$400,000 per year for up to 5 years

Key Personnel Costs:

- ***PD/PI Effort Commitment***

- Contact PD/PI: minimum effort: 2.4 person-months (20%).
- Multiple PD/PI: each PD/PI: minimum effort of 1.2 person-months (10%)
- Levels cannot be reduced during the project period.

- ***Protocol Chairs and Protocol Statistician Effort Commitment***

- Substantial efforts: e.g., minimum 1.2 person-months (10%).
- Research Base PD/PI can serve in a dual role as Protocol Chair/Statistician for one trial; these efforts should be in addition to those expended for PD/PI role

‘CASCADE’ Network FOAs: Budget:
UG1 Research Base: [RFA-CA-21-046](#)

Maximum Direct Costs: \$400,000 per year for up to 5 years

Functional Areas:

- ***Scientific and statistical leadership*** for ‘CASCADE’ protocols:
 - Personnel support (salaries, consultant charges etc.) for all scientific investigators.
- ***Operational oversight*** for ‘CASCADE’ protocols:
 - Personnel support (salaries, consultant charges, etc.) for all administrative staff who will oversee the implementation of the clinical trials at diverse set of domestic and international sites.
 - Costs to develop and implement procedures for ensuring compliance with various regulatory and administrative reporting requirements
- ***Training and Capacity Building*** in the ‘CASCADE’ Network:
 - Costs related to providing training and capacity building activities for staff and trainees at the local institutions and intended-use settings where the studies are being conducted.

‘CASCADE’ Network FOAs: Budget:
UG1 Clinical Sites: [RFA-CA-21-047](#)

Maximum Direct Costs: \$400,000 per year for up to 5 years

Key Personnel Costs:

- ***PD/PI Effort Commitment***
 - Contact PD/PI: minimum effort: 2.4 person-months (20%).
 - Multiple PD/PI: each PD/PI: minimum effort of 1.2 person-months (10%)
 - Levels cannot be reduced during the project period.
- ***Personnel for 2-4 clinical trials (ranging widely in scope, geographic settings, and sample size)***
 - Clinical and scientific staff
 - Administrative and clinical research staff

‘CASCADE’ Network FOAs: Budget:
UG1 Clinical Sites: [RFA-CA-21-047](#)

Maximum Direct Costs: \$400,000 per year for up to 5 years

- **Leveraging ongoing cervical cancer prevention service delivery programs**
 - Most standard-of-care costs would be covered by service delivery programs including costs for screening tests (e.g., visual inspection-based screening) and precancer treatment equipment (e.g., portable thermal ablators or cryotherapy devices).
 - Relevant costs for implementing clinical trial-specific procedures may be included in the budget.
- **Budget line item of at least \$25,000 per year under 'Other Costs'**
 - to cover various novel/experimental interventions (e.g., interventions not already covered by the current standard of clinical care activities including any novel point-of-care HPV tests, newer self-sampling devices, novel screening/imaging devices, newer precancer treatment devices, etc.)
 - details not known at the time of the application (and will be known only after the protocols are approved after the network is formed).

‘CASCADE’ Network FOAs: Other Key Application Preparation Guidance

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

- Applicants are ***not expected to propose specific concepts and protocols*** as part of their applications in response to these three FOAs.
- Please note that under Section IV.2 in the ‘PHS Human Subjects and Clinical Trials Information’, applicants are not required to complete a study record (i.e., not expected to present details of individual trials) and are only required to indicate that ‘Multiple Delayed Onset Studies’ will be conducted through the ‘CASCADE’ Network.
- However, in their application, ***UG1 Research Base applicants may provide illustrative examples of potential clinical trials*** that could be conducted within the specified areas of research focus of the ‘CASCADE’ Network.
- Coordination between potential applicants for the three FOAs of the U24 Coordinating Center, UG1 Research Bases and UG1 Clinical Sites is ***not expected*** prior to application.
 - The ‘CASCADE’ Steering Committee, composed of successful applicants from each of the three FOAs and NCI staff, will review and prioritize clinical trial concepts and selection of implementation sites for individual studies after the ‘CASCADE’ Network is constituted.

‘CASCADE’ Network FOAs: Other Key Application Preparation Guidance

U24 Coordinating Center: [RFA-CA-21-045](#), **UG1 Research Base:** [RFA-CA-21-046](#), **UG1 Clinical Sites:** [RFA-CA-21-047](#)

“Clinical Trials Required”: Section IV.2: Study Record: PHS Human Subjects and Clinical Trials Information

- All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions: **Only choose 'Delayed Onset Study'**
- Study Title--use: **"Multiple Delayed Onset Studies"**
- Justification Attachment:
 - Applicants are **not** expected to propose specific concepts and protocols as part of their applications in response to these three FOAs.
 - **Only indicate** that the ‘CASCADE’ Network clinical trials will be designed by the UG1 Research Bases and implemented at the UG1 Clinical Sites with assistance and oversight from the U24 Coordinating Center and NCI during the Project Period. Each clinical trial concept developed will be subject to approval through the ‘CASCADE’ Network Steering Committee and each protocol will be subject to approval by the NCI Oversight Committee prior to activation. The Coordinating Center will participate for providing infrastructure support for scientific review and program coordination, data management, and independent risk-appropriate auditing for network clinical trials.

Additional Budget Instructions:

The following costs should **not be** included in the budget:

- Costs associated with routine patient care that are reimbursable by insurance.
- Costs for alterations and renovations.

'CASCADE' Network FOAs: Other Key Application Preparation Guidance

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

- PDs/PIs of applications submitted in response to any of the three individual FOAs ***must not be named*** as Senior/Key Personnel or Other Significant Contributors on any teams submitting applications to the companion FOAs.
- NCI's goal is to maximize participation of diverse institutions and permit applicants to tailor applications to their most suitable expertise/organizational elements.
 - Clarifications:
 - There is no limitation in the FOAs regarding multiple applications within one FOA.
 - An investigator may be a PD/PI and/or Key Personnel/Significant Contributor in applications responding to the same FOA type.
 - This, of course, will need appropriate justifications regarding effort and scientific and budgetary overlap between the applications.
 - Example:
 - Dr. XYZ is a multiple PI on an application for RFA-CA-21-046 (UG1 Research Bases) from institution A.
 - Dr. XYZ cannot be named as an Investigator on an application to FOA RFA-CA-21-047 (UG1 Clinical Sites) from Institution B.
 - However, Dr. XYZ can serve as a Key Personnel on an application to FOA-CA-21-046 (UG1 Research Bases) from Institution C (but will need appropriate justifications to address effort and overlap).

'CASCADE' Network FOAs: Other Key Application Preparation Guidance

U24 Coordinating Center: [RFA-CA-21-045](#), **UG1 Research Base:** [RFA-CA-21-046](#), **UG1 Clinical Sites:** [RFA-CA-21-047](#)

U24 Coordinating Center

- Organizational and coordination hub
- US PI(s)-led, self-organized, multi-disciplinary team of US- and/or LMIC-based domain-specific experts in
 - network-wide coordination and facilitation of scientific review
 - centralized data management support
 - independent risk-appropriate auditing
- Multi-disciplinary expertise in program and operations management, clinical research informatics/information technology, and clinical trials auditing

UG1 Research Bases

- Scientific and statistical hubs
- US PI(s)-led or LMIC-based PI(s)-led self-organized, multi-disciplinary consortium with complementary expertise (clinical effectiveness, HPV/cervical cancer prevention and control, HIV/AIDS care, and gynecology/women's health/reproductive health).
- Leadership for developing, implementing, and analyzing multi-institutional pragmatic clinical trial protocols.

UG1 Clinical Sites

- On-site implementation leadership
- LMIC Sites: led either by LMIC PI(s) or co-led by LMIC and US-based PI(s)
- US Sites: led by US PI(s).
- Self-organized consortium of clinicians and/or clinical investigators with expertise and experience in providing clinical care or cancer prevention services to patients and/or communities in collaborative, multi-institutional clinical trials.

'CASCADE' Network FOAs: Application Review Information

U24 Coordinating Center: [RFA-CA-21-045](#), **UG1 Research Base:** [RFA-CA-21-046](#), **UG1 Clinical Sites:** [RFA-CA-21-047](#)

Applications submitted to the NIH in support of the [NIH mission](#) are evaluated for scientific and technical merit through the NIH peer review system.

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the scored and additional review criteria (as applicable).

For additional review details, please refer to the individual FOAs

Scored Review Criteria

- Significance
- Investigator(s)
- Innovation
- Approach
- Environment

Additional Review Criteria

- Study Timeline
- Protections for Human Subjects
- Inclusion of Women, Minorities, and Individuals Across the Lifespan
- Vertebrate Animals
- Biohazards

'CASCADE' Network FOAs

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

Key Dates

- (Optional) Letter of Intent Due Date: November 28, 2021
- **Application Due Date: December 28, 2021**
- Scientific Merit Review: March 2022
- Advisory Council Review: May 2022
- Earliest Start Date: July 2022

'CASCADE' Network FOAs

U24 Coordinating Center: [RFA-CA-21-045](#), UG1 Research Base: [RFA-CA-21-046](#), UG1 Clinical Sites: [RFA-CA-21-047](#)

For additional questions, please see: <https://prevention.cancer.gov/cascade>

or

email cascade@mail.nih.gov

or

email

Dr. Vikrant Sahasrabuddhe, Program Director, NCI Division of Cancer Prevention,
at sahasrabuddhevv@mail.nih.gov



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