Part I - Overview Information

Department of Veterans Affairs

Participating Organizations
Veterans Health Administration, Office of Research and Development (VA-ORD)

Forms of Participating Organizations
Clinical Science Research and Development (CSRD) Service

Title
Precision Oncology Actively Managed Portfolio Clinical Trials (I01)

Announcement Type
New

Catalog of Federal Domestic Assistance Number:
64.054

Note:
- Hyperlinks direct the applicant to information and resources whenever possible.
  - Blue hyperlinks redirect the applicant to other sites within this document and to outside information that is accessible to the public.
  - Red hyperlinks are only accessible using the VA intranet environment.

Request for Applications (RFA) Number: CX-23-004

Key Dates
Release/Posted Date: November 15, 2022

Letter of Intent: A letter of intent is required for this funding opportunity. Letter of intent guidance and templates may be found: https://www.research.va.gov/services/shared_docs/resources.cfm#4. See the ORD Submission Calendar for submission dates.

Application Deadlines, Submission, Peer Review, and Start Dates: See Table 3.

Expiration Date: December 31, 2023

Application Instructions: Applications submitted in response to this RFA must be submitted electronically to Grants.gov using the VA SF424 Research and Related (R&R) Forms (VA-SF424) as described in the SF424 (R&R) Application Guide for VA-ORD (VA-SF424 AG).

This RFA must be used in conjunction with the VA version of the Application Guide SF424 (R&R) available on the VA-ORD Intranet site. The instructions in this RFA may differ from, and supersede, the general instructions contained in the VA-SF424 AG.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

Precision oncology (PO) is about applying the most appropriate treatment to the right patient at the right time informed by an understanding of the relevant molecular characteristics of the patient and their cancer. Precision oncology incorporates patient genetic information, tumor genomic and clinical data, molecular-driven precision tumor targeting, as well as other unique personalized or tumor specific information that may to inform risk prediction, diagnosis, treatment, and response.

Awards under this RFA will focus on precision oncology-based approaches to clinical trials with emphasis on studies to impact clinical practice and inform healthcare decision making. The studies will be part of the Precision Oncology Actively Managed Portfolio (PO AMP). PO AMP is one of the VA Research Enterprise transformation initiatives. **This RFA is open to applications from all ORD research services provided the proposed clinical trial is within the scope of precision oncology,** is specific for single-site or multi-site clinical trials that can be concluded within the stated funding limits **and qualifies for one of the two types of accelerated review described below. During scientific peer review, reviewers will be selected with the appropriate expertise to match the discipline of the proposed research. All applications under this RFA will be administered through CSR&D.**

Applications under this RFA will utilize enterprise-wide infrastructure, teams with multidisciplinary expertise, resources, strengths of facilities and patient population to focus on studying the most important clinical interventions that will advance care for Veterans' healthcare needs. The proposed clinical trial should be novel, feasible, address a high clinical need, have a high impact, and can be implemented in the healthcare system or can inform decision making.

For this RFA, 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 the interventions on biomedical, behavioral or functional health-related outcomes.

Qualifications for Accelerated Review

This RFA will utilize an accelerated review and selection process to address specific and urgent research questions deemed as high clinical priority provided the proposed study aligns with (1) an urgent need for information to treat cancer, or (2) the achievement of longer collaborative goals requires a specific finding to progress. Studies considered for accelerated review will be based on the intimate understanding of clinicians and researchers of the knowledge gaps in areas required to advance precision oncology clinical care and likely would have been discussed and supported in one of the AMP workgroups (Example: Precision Oncology AMP will utilize Lung Precision Oncology Program, Precision Oncology Program for Cancer of the Prostate, Genitourinary workgroups, and scientific concept review panels), or another similar consortium supported/recognized by the National Oncology Program Office/Specialty Care or VHA clinical operations.

Accelerated review is only available for clinical trials that are specifically focused on precision oncology and meets the accelerated review criteria outlined in this RFA listed below. This RFA will utilize two types of review, accelerated and critical accelerated:

Accelerated Review Qualifications
Accelerated review applies to research that is an ORD priority that immediately requires specific knowledge to achieve results. Research proposals eligible for accelerated review:

- Have the potential for immediate and/or direct impact on clinical care or clinical decision making;
- Are pilot studies that are responsive to critical clinical problems that require initial findings to establish evidence for a robust priority project and endorsed by an AMP workgroup or clinical/VHA leadership (i.e., when the achievement of longer, collaborative goals require a specific finding to progress);
- Address topics that urgently respond to an issue of importance to the Veteran population.

Critical Accelerated Review Qualifications
Critical accelerated review will be reserved for research that addresses an urgent need for information to treat an illness. This review process is intended only to be used in instances where research needs to begin as soon as possible. Research proposals that qualify for critical accelerated review:

- Have high Congressional, Presidential, ORD, or clinical operations relevance or priority;
- Address cancer that requires immediate action to reduce high hospitalization, mortality, and morbidity rates.

Note, this RFA is not open to applicants wishing to receive accelerated review for applications under the normal Merit Review process.

Eligible applicants should describe how their proposal directly aligns with precision oncology and are encouraged to submit innovative or highly impactful, clinically relevant research with the potential to significantly advance real-world clinical care for Veterans and/or inform policy decision making for the healthcare system. Examples of **priority research areas** of specific interest to PO AMP include:

- Precision-based approaches to cancer screening and/or prevention
- Precision-based approaches to health disparity, access, equity and inclusion, and patient safety
- Precision-based approaches to improve quality of life and survival through appropriately supported escalation or de-escalation therapeutic strategies
- Precision-based approaches to physical activity on cancer treatment, prognosis, recurrence and survival
- Application of innovative technologies/tools (e.g., artificial intelligence, machine learning, neural networks/algorithms) to stratify patients for risk stratification, treatment management and monitoring, and/or inform clinical decision making (decision support tools)
- Novel approaches to target rare cancers and/or rare subtypes
- Precision medicine especially individual treatment response, including biomarker-driven/molecular and other targeted approaches

Clearly identified milestones and deliverables should be developed for the proposed project. ***The inclusion of early career and underrepresented investigators in research teams and opportunities for leadership is highly encouraged.***

This RFA is directed solely to clinical trials as described in the required letter of intent (LOI). Applications should specifically address issues of safety, recruitment of Veteran participants, and adequate statistical power to obtain clinically meaningful results. Clinical projects that involve assessments of diagnostic approaches designed to show the equivalence of test results with those of existing diagnostic devices or methods will not be considered as interventional clinical trials for funding under this RFA. An approved LOI for Clinical Trials is required for all applications to this RFA.

The Senior Portfolio Manager for PO AMP (in consultation with the ISRM Deputy CRADO) will determine the appropriateness for PO AMP support based on factors such as purview, relevance and portfolio balance. Applications that do not fall within the PO AMP purview may be returned without scientific peer review.

Precision Oncology Actively Managed Portfolio

The PO AMP is a portfolio of related research that prioritize communication, coordination, and collaboration between clinicians, researchers and other stakeholders to solve specific real-world questions that are important to Veterans, providers, and/or the healthcare system. Consequently, the PO AMP will strategically identify and support research that seeks to answer specific, real-world questions that results in the improvement of health, care and well-being of Veterans; maximize research investments to produce real-world impact, coordinate and collaborate with VHA clinical operations and external partners to address high priority clinical issues faced by Veterans informed by the clinicians who are treating them. PO AMP aims to maximize efficiency by supporting research projects end-to-end, develop and implement quality improvement interventions that enhance research outcomes in support of portfolio goals, accelerate translation into the clinic and ensure implementation of findings. ORD has developed a national cancer clinical research enterprise with expertise in various cancers including genitourinary, lung, colon and others through various national and regional networks, and leverages partnerships with federal and philanthropic entities in several areas to accelerate genomic, molecular and epidemiological understanding of how genes, proteins and other markers influence cancer progression, prognosis and outcomes. PO AMP will build on these efforts through research to establish the evidence to ensure Veterans have access to systematic and equitable high quality oncology care.

Section II. Award Information

1. Mechanism of Support

This RFA describes the VA Merit Review Award Program, which is an intramural funding mechanism to support investigator-initiated research conducted by eligible VA investigators at VA Medical Centers (VAMCs) or VA-approved sites. Merit Review Awards are ORD's principal funding mechanism.

Applications electronically submitted for PO AMP through Grants.gov will be peer-reviewed by a Scientific Review Group (SRG) to provide the ISRM Deputy CRADO with an evaluation of the scientific merit of the proposed research, including recommendations on budgets, funding

durations, and potential ethical concerns. All funding decisions are made by the ISRM Deputy CRADO.

Regulatory Review Process for Accelerated Proposals: Although the regulatory review process can cause delay due to its rigid structure, investigators with an approved LOI for proposals designated for accelerated reviews are expected to have a completed research protocol developed by the time of application submission, no exceptions. The LOI approval letter will provide additional guidance to investigators for pre-consultation and pre-review of research protocols (IRB).

Applications submitted to the PO AMP for accelerated review are expected to begin developing all applicable regulatory and research compliance approvals for Just-in-Time (JIT) submission as outlined in the approved letter of intent (i.e., prior to being notified of the application being selected for funding). Before funds are released, all applicable regulatory and research compliance approvals must be obtained locally and submitted to the JIT) system. JIT requires the local assurance forms to ensure all VA regulations and policies are met. Ideally, JIT requirements should be completed and uploaded within a short window after application selection to ensure rapid start-up of the project and execution of research funding. **Approval for funding may be withdrawn for applications that fail to clear JIT within 60 days.** All Specific Aims of an application must be able to be cleared in JIT. If a portion of the application is not ready for JIT clearance, the funding decision may be rescinded.

2. Application Types Allowed

New: Proposals that have not been previously reviewed or funded by ORD.

Resubmissions: Only one revised application (Resubmission) is allowed if the initial submission is not selected for funding. All Resubmissions must include a brief introduction that addresses the concerns raised in the previous review. If an application is not funded after resubmission, it is not eligible to receive funding. The Program Director (PD)/Principal Investigator (PI) will require a new approved LOI with "New" Specific Aims prior to submitting an application. **"New" applications submitted without significantly new Specific Aims will be withdrawn from review.**

Renewals: Clinical Trial Awards cannot be renewed.

3. Multiple Awards and Submissions

An investigator may submit concurrent applications to more than one PO AMP RFA, though they cannot be a PD/PI (either Contact PD/PI or one of multiple PD/PIs) for more than one application to the same RFA per review cycle. An investigator may submit applications to a maximum of three CSR&D RFAs in any given review cycle.

Submitting multiple applications with similar subject matter to different PO AMP RFAs may result in the applications being assigned to the same SRG; if this occurs requests to move one of the applications to a different SRG will not be entertained.

4. Funds Available

Merit Review Clinical Trial Award Budget Cap and Duration:

Budget Item	Limit for Single Site	Limit for Multi-Site
Budget Cap	• For 2 years, $600,000 • For 3 years, $900,000 • For 4 years, $1,200,00	For a **2-site** a total: • For 2 years, $600,000 • For 3 years, $1,125,000 • For 4 or 5 years, $1,500,000 • Additional $100,000 per site per year for each additional site.
Duration	Up to 4 years	Up to 5 years

The salary for a non-clinician contact PD/PI identified in Box 14 of the *VA-ORD* SF424 (R&R) Cover Form is included in this cap.

Salary increases (cost of living adjustments - maximum of 2% per year) are permitted for all current VA salaried personnel (including the contact PD/PI), and may be budgeted in out years. Cost of living adjustments are not permitted for any other budget category; including Intergovernmental Personnel Act agreements (IPAs). Cost of living adjustments may not be used to exceed the total project budget cap. Salaries are to include actual fringe benefits for all current VA salaried personnel and no more than 30% fringe benefits for all "to be determined" positions.

Exceptions to the Budget Cap and/or Duration: Applications may only exceed the budget and duration requirements if the *Letters of Support* (LOS) section includes a copy of the Letter of Approval for a waiver. Rare exceptions to the budget cap and/or maximum duration may be granted prior to application submission for fully justified and compelling circumstances. Waiver requests must be submitted by the local R&D Office to vhacoblcsrdrev@va.gov. Deadlines for submission are in Table 3.

5. Cost Sharing or Matching Funds

Not Applicable

6. Location of Research Space

All performance sites (VA and non-VA) must be included in the *Project/Performance Site Locations Form of the VA-ORD SF424*. Provide a detailed description of the institutional facilities and resources available to the project. Specify the campus location (VAMC or affiliate) for each facility and resource cited.

PD/PIs are expected to perform VA-funded research within a VA facility or VA-leased space that they control. If any of the proposed work will be carried out in non-VA space controlled by a PD/PI or other VA investigator, they must obtain a waiver to perform the research off-site before beginning work done in an off-site space. Work performed in a non-VA collaborator's off-site

laboratory or off-site Core Facility does not require an Off-site Waiver, except when a VA investigator is the Core Facility Director. If available, a copy of the approval letter for the Off-site Waiver should be included in the Letters of Support attachment (refer to Program Guide 1200.16).

7. Duplicate Submissions

This RFA is specific to Precision Oncology Actively Managed Portfolio and duplicate submissions in part or whole will not be accepted. All applications in response to the PO AMP RFA must be submitted to CSR&D.

Section III. Eligibility Information

1. Eligible Institutions

Applications may be submitted from any VAMC with an active Federalwide Assurance (FWA) of compliance with the US federal regulations for the protection of human subjects in research.

2. Eligible Individuals

The Merit Review Award Program is an intramural program to fund research conducted by VA-salaried investigators at VAMCs or VA-approved sites. A PD/PI shall hold an MD, PhD, or equivalent doctoral degree in a medical, biological, or behavioral science field. All PD/PIs must have a VA paid appointment of at least 25 hours per week (5/8ths) to receive ORD research funding (VHA Program Guide 1200.15). Contract clinicians are not VA employees. Given the desire to expedite start-up of funded projects, PD/PIs must have a VA paid appointment at the time of application.

The VA employment status, including 8^{ths} appointment of each PD/PI must be indicated in the Letter of Support from the Medical Center Director. If a PD/PI is currently less than 5/8ths VA paid appointment, the LOS from the Medical Center Director must include a commitment to offer the PD/PI a 5/8ths (or greater) appointment at the VAMC if the application is approved for funding. PIs (or MPIs) must demonstrate the following:

- Expertise in (1) relevant translational and clinical research and/or (2) cancer diagnosis or treatment;
- Knowledge of VA cancer patient population for their respective facility/region;
- Strong leadership capabilities in clinical, scientific and operational management (e.g., methodology, recruitment, regulatory affairs and personnel management, screening, big data, and/or clinical trial program); ***consideration will be given to early career investigators with prior history that demonstrate leadership potential;***
- Previous success in building and establishing programs that require senior; leadership/administration support and leveraging of resources (experience working with local VA leadership is strongly encouraged);
- A record of working collaboratively and engaging a broad range of stakeholders, including VA research enterprise, academic affiliates and industry partners.

The PD/PI must be current with all requirements related to intellectual property (VA invention documents and certifications), submission of annual progress reports (Research Performance

Progress Reports (RPPRs)) and Final RPPRs, clinical trials registration, and clinical trials results reporting for existing and previous awards.

Multiple PD/PIs: The "Contact" PD/PI identified in the VA-SF424 Cover Form will be responsible for all communication between the PD/PIs and VA-ORD. Only individuals assigned the PD/PI role in the Budget Form and the Key Personnel Form are considered PD/PIs.

Applications proposing more than one PD/PI must include a full justification in the *Multiple PD/PI Leadership Plan* section; each of the multiple PD/PIs (MPI) must be assigned the PD/PI role. *NOTE:* **Investigators should be designated as "MPI" in the e-application, NOT "Co-I/MPI." Incorrectly designating a Co-PI/MPI may lead to the administrative withdrawal of the application.** The terms Co-PD and Co-PI are no longer recognized by eRA or VA-ORD.

Site investigators must also meet the eligibility requirements described above.

Section IV. Application and Submission Information

The local R&D Service must complete several registration processes before submission of an electronic application (see Section 2.2 of the *VA-ORD SF424*). Applications must be submitted to Grants.gov by the local research Signing Official (SO). Applicants are highly encouraged to start the submission process well in advance of the submission deadline to ensure the application passes the validations performed in Grants.gov and the eRA.

1. Request Application Information

See the *VA-ORD SF424* for step-by-step guidance.

2. Content and Form of Application Submission

Prepare all applications using the SF424 (R&R) application forms with the VA-ORD Application Guide SF424 (R&R) found at http://vaww.research.va.gov/funding/electronic-submission.cfm and this RFA.

A summary of the main components required for this application is shown below in Table 1. Table 2 below contains *VA-ORD SF424* instructions specific to this RFA. Instructions in Table 2 are in addition to, or supersede, instructions in the VA-ORD SF424 AG as appropriate.

Guidance specific for this RFA:
Unless otherwise noted in this RFA, all instructions contained in the VA-ORD Application Guide SF424 (R&R) must be followed. Failure to follow instructions may cause delays in submission or withdrawal of applications from review.

Research and Related Other Project Information Form
Table 2 below contains descriptions of the required files that must be attached to Item 12 "Other Attachments" of the Research and Related Other Project Information Form. For guidance on the creation of attachments and format specifications see the VA-ORD Application Guide SF424 (R&R) on the VA-ORD Intranet at http://vaww.research.va.gov/funding/electronic-submission.cfm.

*Note: The file names for Attachments #1-10 are **mandatory** and may not be changed. **Altered file names will cause an error to be generated**. Only the descriptor in the file names for Appendices #11, 12, 13… etc., may be changed. Altering any other part of the file name may result in parts of your application being excluded from the final electronic image that the reviewers receive or for the attachments to appear in the wrong order.*

All applications must be self-contained (i.e., without use of URLs or video clips) within specified page limits. Internet website addresses (URLs) and video clips may not be used to provide information necessary to the review. URLs may only be placed in the Biographical Sketch and Bibliography and References Cited attachments.

Additional Information about Clinical Trial Applications
Applicants should upload a single attachment for each appendix that includes the following information relevant to the proposed clinical trial. It is recommended that these appendices include no more than 4 pages. Applicants should use the headers below in their description.

Recruitment and Retention:
- Recruitment and Referral sources, including detailed descriptions of the census/rate of new cases and anticipated yield of eligible participants from each source;
- Procedures that will be used to monitor enrollment and track/retain participants for follow-up assessments;
- Strategies that will be used to ensure a diverse, representative sample;
- Potential recruitment/enrollment challenges and strategies that can be implemented in the event of enrollment shortfalls (e.g., additional outreach procedures, alternate/back-up referral sources);
- Evidence to support the feasibility of enrollment, including descriptions of prior experiences and yield from research efforts employing similar referral sources and/or strategies.

Milestones and Timelines:
- Objective, quantifiable, and scientifically justified milestones;
- A proposed timeline for reaching important study milestones such as: (a) finalizing the study procedures and training participating clinical site staff; (b) finalizing the intervention manual and assessment protocols, including fidelity measures/procedures, where applicable; (c) enrolling 25%, 50%, 75% and 100% of the sample; (d) completing all subject follow-up assessments and data collection activities, including data quality checks; (e) analyzing and interpreting results; and (f) preparing de-identified data and relevant documentation to facilitate data sharing, as appropriate.

Multi-Site Management Plan:
- How sites and investigators will be selected;
- How procedures, data analysis, and data storage will be integrated across different sites and elements within a project. Plans should address data management, reliability and quality control;
- How the overall managerial and administrative responsibilities will be divided in a team (i.e., which laboratory will coordinate various parts of the project and which will be responsible for overall coordination), as well as leadership and joint decision-making;
- What procedures will be used to assure sharing of resources across laboratories in the team, as well as reliability and quality control of data and resources as appropriate and consistent with achieving the goals of the program;

- How close collaboration, coordination, and effective communication will be maintained among laboratories in a team through regular meetings (in person/teleconference). This plan should include frequency and types of contact between participating researchers, and documenting and disseminating group meeting proceedings;
- The plans for project data coordination, including standards and integration, quality control, issues with missing data and plans for ensuring comprehensive transparency of data reporting/sharing across sites, as appropriate and consistent with achieving the goals of the program;
- The plans for ensuring experimental rigor and control of bias (e.g., with sample size estimation, data handling), as appropriate;
- The plans for completion of the research project should a key member leave the group, including plans to replace the PD/PI, if needed;
- The plans for publication and authorship rights and a process for arbitrating disagreements on publication and other issues among linked applications.
- Performance requirements for sites and plans for remediation when a site does not meet targets for enrollment or other performance requirements

Table 1. Summary of Required Forms and Attachments

Forms, Attachments, and Templates with Size Limits as Applicable	Required When?	VA-SF424 Instructions
SF424 (R&R) Form	Always	Section 3.2
Project/Performance Site Locations Form	Always	Section 3.3
Research and Related Other Project Information Form:		Section 3.4
Project Summary/Abstract (40 lines of text)	Always	
Project Narrative (10 lines of text)	Always	
Bibliography & References Cited (4 page limit)	Always	
Facilities & Other Resources	Always	
Equipment	Always	
Other Attachments:		
1. Introduction to Revised Application (3 page limit)	Resubmission	
2. Specific Aims (1 page limit)	Always	
2a. Research Plan (14 page limit)*	Always	
3. Progress Report (5 page limit)*	Always†	
4. Human Subjects	Always	
5. Vertebrate Animals	If Applicable	
6. Multiple PD/PI Leadership Plan	If Applicable	
7. Consortium/Contractual Arrangements	If Applicable	
8. Signed Directors Letter*	Always	
8b. Letters of Support	If Applicable	
9. Data Management and Access Plan	Always	
10. Financial Disclosure	Always	
Appendices:*		
11. List of Appendix Items*	Always	
12. List of Abbreviations*	Always	
13. SRG Request*	Always	
14. LOI Approval Memo*	Always	
15. Recruitment and Retention*	Always	
16. Milestones and Timelines*	Always	
17. Multi-Site Management Plan*	If Applicable	
18. Investigational New Drug*	If Applicable	
SF424 (R&R) Senior / Key Person Profile(s)	Always	Section 3.5
SF424 (R&R) Budget	Always	Section 3.7
SF424 Summary Budget Worksheet	Always	Section 3.7

* These sections have special instructions for this RFA that are in addition to or supersede instructions in the VA SF424. See Table 2 below.

† New applications from previous awardees require a progress report. See Table 2 below.

Table 2. RFA Specific Instructions for VA SF424 Forms and Attachments

Form/Attachment Name **Page Limit** ***Required File Name***	**Instructions**
2a. Research Plan **14 Page Limit** *02a_VA_Research_Plan.pdf*	The Research Plan must include sufficient information for evaluation of the project, independent of any other document (e.g., previous application). Be specific and informative. In general, the Research Plan should include the following sections: **Background and Significance** Briefly sketch the background leading to the present application, critically evaluate existing knowledge (e.g., published literature, etc.), and specify the gaps that the project is intended to fill. State concisely the importance and Veteran health relevance of the research described in this application. Relate the specific aims to the broad, long-term objective of improving Veteran health. If the aims of the application are achieved, state how scientific knowledge or clinical practice will be advanced. Additionally, describe the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive the field. **Preliminary Studies** Use this section to provide an account of the PD/PI's preliminary studies pertinent to this application. This information will also help to establish the experience and competence of the investigator to pursue the proposed project. Pilot data demonstrating the feasibility of obtaining samples, recruiting subjects, and/or data needed for the project must be included, if applicable. **Research Design and Methods** Describe the research design framework, procedures, and analyses to be used to accomplish the specific aims of the project. Include how the data will be collected, analyzed, and interpreted. Describe any new methodology and its advantage over existing methodologies. Describe any novel concepts, approaches, tools, or technologies for the proposed studies. Describe steps that will be carried out to minimize subjective bias (e.g., randomization, experimental and control group matching, blinded assessment of outcomes, etc.). Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. As part of this section, provide a timetable for the project. Point out any procedures, situations, or materials that may be hazardous to personnel

Form/Attachment Name **Page Limit** ***Required File Name***	**Instructions**
	and the precautions to be exercised. Provide characteristics related to inclusion/exclusion criteria and inclusion of sub-populations, as well as a description regarding Veteran participation. Non-Veteran enrollment must be approved by CSRD; please see our Participation of non-Veterans in CSRD-Funded Studies Frequently Asked Questions. Describe assumptions related to sample size and provide power analysis to support inferences. Include a description of how Veterans were consulted regarding the design and significance of this proposed work, and how that information influenced or changed any elements of the study supporting feasibility and relevance of work proposed.
3. Progress Report **5 Page Limit** *03_VA_Prog_Report_Pubs.pdf*	Progress Reports are required for all applications from a PI who has had any VA funding including on-going or completed Merit or Career Development from any VA-ORD Service.
4. Human Subjects **No Page Limit** *04_VA_Human_Subjects.pdf*	A Targeted/Planned Enrollment Table must be included. All subjects included in the trial should be Veterans. Any proposed enrollment of non-Veterans must be approved at the LOI stage.

Form/Attachment Name **Page Limit** ***Required File Name***	**Instructions**
8. Signed Directors Letter *08_VA_Director_Letter.pdf*	A signed (e-signature accepted) and dated (within the last year) Letter of Support from the VAMC Director is required and must include the following: • A statement that the Director understands the impact of the proposed research on the facility's organization and that he/she endorses the project. • An explicit statement of where research will be conducted, whether it is in VA space, VA-leased space, or space at the affiliate; that appropriate off-site waivers have been requested, and that the VA space described in the application and necessary support of the VA facility will be available. • If human samples are used, an explicit statement of source of samples. • State the current VA employment status of the PI, including 8ths. • The Director's memorandum must contain a statement indicating that the PD/PI will be given a VA-paid appointment of at least 5/8ths time. ***Given the desire to expedite start-up of funded projects, PD/PIs must have a VA paid appointment at the time of application***. NOTE: For multiple PD/PI applications where the PIs are at different VAMCs, a letter from each VAMC Director is required. **Applications submitted without this signed letter attachment will not be accepted for review.**
11, 12, 13… Appendices *11_VA_Appendix_1.pdf* *12_VA_Appendix_2.pdf* *13_VA_Appendix_3.pdf* (additional attachments as needed: same file name format)	See the VA-ORD Application Guide SF424 (R&R), Attachments for Item 12, for guidance on content and naming of files of appendices. **Appendices must be uploaded in the order in which you wish them to appear in the e-application. To check for the correct ordering of attachments, review the Bookmarks and Table of Contents (ToC) within the final e-application.** The first appendix should be a summary sheet listing all of the items included in the appendices; it should be named: **"11_VA_Appendix_1_List of Appendix Items.pdf."**

Form/Attachment Name Page Limit ***Required File Name***	**Instructions**
	The second appendix should be the alphabetized list of abbreviations used in the application; it should be named: **"12_VA_Appendix_2_Abbreviations.pdf."** The third appendix should be a brief document stating what panel the PD/PI would like the application assigned; no other information should be included in this document. The document should be named: **"13_VA_Appendix_3_SRG Request.pdf"** *(All PO AMP accelerated review applications should be assigned to SPLP review panel.)* The fourth appendix should be a copy of the approved LOI Approval letter; it should be named: **"14_VA_Appendix_4_LOI Approval Memo.pdf"** The fifth appendix should provide a clear description of participant recruitment and retention procedures; it should be named: "**15_VA_Appendix_5_Recruitment and Retention.pdf**" The sixth appendix should provide a clear description of milestones and timelines: it should be named: "**16_VA_Appendix_6_Milestones and Timelines.pdf**" The seventh appendix should be a plan detailing the measures that will be taken to ensure cross-disciplinary communication and integration across the team; it should be named: "**17_VA_Appendix_7_Multi-Site Management Plan.pdf**" The eighth appendix, if needed, should be the IND for a submission that includes a drug study; it should be named: "**18_VA_Appendix_8_IND.pdf**" Additional appendices can be added using the file name conventions described above. Please refer to the SF424 AG for guidance on allowable appendix attachments.

Summary Budget Worksheet and R&R Budget Form

Budget Guidance
See the VA Application Guide SF424 (R&R), Section 3.7 Summary Budget Worksheet and R&R Budget Form for guidance on budget content for Sections A-L. Both of these forms are mandatory for each application.

Personnel (Section A): For a non-clinician PD/PI enter the calendar months that indicate the actual effort that the investigator will expend for the research described in this application only; salary consistent with their total VA effort may be requested. Describe the PD/PI's contribution to the proposed research, as well as the other activities comprising their total VA effort, in the Budget Justification section.

If the PD/PI is a Research Career Scientist, enter the calendar months that indicate the actual effort that the investigator will expend for the proposed research, but do not include salary in the budget. In the Budget Justification section discuss the investigator's contribution to the proposed research only.

Salary support may be requested only for activities that are uncompensated from other sources, such as the academic affiliate or other funding agencies. Any differences in the calendar months effort for the work proposed and total VA effort (salary support) must be fully described in the budget justification.

Personnel (Section B): The last row of Section B should include all VA personnel involved in the project, except the PD/PI named in Section A.

Applications with Multiple PD/PIs: When multiple PD/PIs are proposed, the Contact PD/PI (identified in Box 14 of the SF424 (R&R) Cover Form) is eligible to receive salary within the budget cap. Identification of multiple PD/PIs may not be used to exceed budget caps. Cost of living adjustments for personnel other than contact PD/PI may not cause the budget to exceed the stated cap.

Other Direct Costs (Section F): All Other Direct Costs described below should be totaled and entered in Section F, Line 8 of the R&R Budget Form. Leave all other fields blank in Section F (1-7, 9, and 10).

3. Submission Dates and Times

Deadlines: Table 3 below contains deadlines for Merit Review Award Program applications.

3.A. Submission, Review, and Anticipated Start Dates

All new or changed/corrected applications must be submitted and accepted (error-free) in Grants.gov on or before 6 p.m. (local time) of the Last Possible Submission Date (submission deadline) in Table 3.

NOTE: Applications accepted by eRA Commons with no errors (with or without warnings) are provided a two-business day examination window to check for errors. The application is automatically verified on the third business day if it is not withdrawn by the SO during the examination window.

Errors will stop an application from proceeding in the system and must be addressed. Warnings will not stop an application from moving forward and may be addressed at the applicant's discretion.

Once verified, an application is considered final and no other version will be accepted for review. It is the responsibility of the PD/PI and AOR/SO to check for errors during the examination window.

Table 3. Standard Dates for Application Deadlines for 2023

SUBMISSION CYCLES:	Winter 2022	Spring 2023	Summer 2023	Fall 2023
Deadline for Letter of Intent and budget cap waiver requests	September 1	December 1	March 11	June 1
First day to submit applications to Grants.gov	November 1	February 1	May 1	August 1
Deadline to submit to Grants.gov (After this date the full two-day correction window cannot be used.)	December 8	March 8	June 8	September 7
Last Possible Submission Date (to Grants.gov) **WARNING:** If you submit an application on the Last Possible Submission Date and errors are identified by either Grants.gov or eRA Commons there may not be enough time to fix the errors, resubmit, and have the application received and verified by eRA. If your application is accepted by eRA with no errors, do not withdraw the application during the two-business day examination window unless there is sufficient time to resubmit a changed/corrected application by the submission deadline. Changed/Corrected applications submitted after the Last Possible Submission Date will not be accepted for review.	December 12 6:00 p.m. local time	March 10 6:00 pm local time	June 12 6:00 p.m. local time	September 11 6:00 pm local time
Review and Award Cycles:	**Winter**	**Spring**	**Summer**	**Fall**
Scientific Merit Review	March	May - June	August	November-December
Administrative Review	April – May	July - August	Sept. – Oct.	January - February
Earliest Project Start Date[§]	July 1	October 1	January 1	April 1

[§]CSRD for the PO AMP may not always be able to honor the requested start date of an application; therefore, applicants should make no commitments or obligations until confirmation of the start date by the awarding service.

3.A.1. Letter of Intent

A letter of intent is required for this funding opportunity. See https://www.research.va.gov/services/shared_docs/resources.cfm for LOI instructions.

3.B. Application Processing

The local Research and Development Office (ACOS and/or AO) is responsible for submitting a notification of any system errors to the eRA mailbox (rd-era@va.gov) prior to the submission deadline (for Grants.gov issues) or validation deadline (for eRA issues). Although eRA will notify the user of errors and warnings, **applicants should not rely solely on system validations to ensure a successful submission.**

Once received, applications will be evaluated for completeness. **Incomplete applications will not be reviewed**. No additional or replacement information will be accepted after the application is submitted unless requested by the Program Review staff. The only exceptions are official Letters of Acceptance for publication of manuscripts submitted by the PD/PI. These must be sent by e-mail to the Review Mailbox (vhacoblcsrdrev@va.gov).

Applications will be withdrawn from review for administrative non-compliance if they do not adhere to the following:

- All applications must be self-contained (i.e., no URLs/hyperlinks) in sections that have specified page limits. **URLs may only be placed in the Biographical Sketches and Bibliography and References Cited attachments**. eRA will notify the user if URLs are found in an application. NOTE: URLs within official documents that cannot be altered, such as letterhead (i.e., LOS attachment) or published articles/manuscripts (i.e., Appendix attachments), will **not** cause a submission to be rejected.
- All applications must contain a *Summary Budget Worksheet*. Instructions for the *Budget Section* can be found in the VA-ORD SF424 and in this RFA. The worksheet template is available at http://vaww.research.va.gov/funding/electronic-submission.cfm. Verify that the total in the *Summary Budget Worksheet* and *Budget Form* match and that the requested budget does not exceed the cap (per year and project total), unless a waiver has been obtained.
- Applications that do not fall within the PO AMP accelerated review criteria may be returned without scientific peer review.

Section V. Application Review Information

An overview of the Peer Review process is described in Part 1, Section 4 of the VA-SF424 AG. The following review criteria will be considered in the review process for applications submitted to this RFA.

1. Review Criteria

Research Project Evaluation Criteria

Significance: Is there a strong scientific premise for the project? Does the proposed study address an important problem or critical knowledge gap in the field and specifically to the Veteran population? How do the research concepts, methods, technologies, treatments,

services, or interventions advance the field? If successful, what is the likely impact of the proposed study on the scientific field and on Veterans' healthcare? Is there a stated translational pathway?

Innovation: Does the application challenge existing paradigms, explore new concepts, methodologies, or technologies, or otherwise exhibit significant creativity? To what degree does the proposed study represent more than an incremental advance on the published literature?

Approach: How well do the logical reasoning, critical review of the literature, and preliminary data support the rationale and the feasibility of the project? Are the hypotheses, aims, experimental design, methods, and analyses (including statistics) well developed? Are appropriate strategies to ensure a robust and unbiased approach presented? Are sample sizes and the statistical methods to obtain them described? Are relevant biological variables, such as species, strain, sex, developmental state (age), and weight considered? Are potential problems, alternative strategies, and benchmarks for success presented?

Feasibility: Is there sufficient evidence to determine that the proposed studies can be successfully completed? If applicable, is there sufficient evidence for successful recruitment and enrollment of subjects? Can the required animal models or samples be attained? Can the proposed study be completed within the duration of the award? Are proposed studies, including animal studies, adequately powered to answer the research questions?

Investigators: Do the PD/PI(s) and other key personnel have the expertise, experience, and record of accomplishments to enable successful completion of the proposed research? If applicable (Multiple PI/PD), how well are the efforts of the investigators and/or research teams integrated and is the collaboration synergistic or complementary? For Renewal applications, has the applicant been productive and shown research progress in the last funding period?

Multiple PD/PI Leadership Plan (if applicable): To what degree are the organizational plan, leadership approach, and roles and responsibilities of the PIs/PD appropriate with regard to expertise, resources, and commitment to ensure the completion of the project? A multi-site clinical trial should have a clear management plan, including site oversight and performance metrics for managing local sites.

Environment: Do the scientific environment, facilities, and resources support the research requirements so as to enable the success of the project? Is there evidence of institutional support reflecting space, equipment, and other unique resources including availability of and access to populations adequate for the project proposed and/or to facilitate collaborative arrangements?

Ethical/Safety Issues: Are there any ethical, human subject, animal use, or biohazard concerns?

2. Other Considerations

In addition to the above criteria, reviewers will consider the following items; however, these items will not influence the overall priority score.

Budget: Are there concerns with the requested budget (amount and duration)? Are there concerns with overlap with other funded projects listed as "Other support" for any of the key personnel? Is there appropriate justification for all categories of the budget?

Sharing Research Data: Is the Data Management and Access Plan or the rationale for not sharing data reasonable?

Resubmission (if applicable)**:** Has the applicant responded to all or only some of the concerns raised in the previous Summary Statement? Are the responses appropriate? Has the application been improved as a result of the revisions?

Biohazards: Are the proposed materials or procedures hazardous to research personnel and/or the environment? Is the proposed protection adequate?

Foreign/international studies: Does the project have any collaborations or involvement of foreign entities?

Select Agents: Is the use of select agents appropriate? Have the appropriate registrations for Select Agent(s) use been obtained? Are the procedures used to monitor possession use and transfer of Select Agent(s) appropriate? Are the plans for biosafety, biocontainment, and security of the Select Agent(s) appropriate?

Protection of Human Subjects: Are the human participant protections from research risk appropriate? Is the protection against risks sufficient? Are there potential benefits of the proposed research to the participants and others? Importance of the knowledge to be gained? Is there appropriate Data and safety monitoring for clinical trials?

Inclusion of Women, Minorities, and Children: Are the proposed plans for inclusion of minorities and members of both sexes/genders appropriate and adequate? The VAMC Director must approve participation in proposed research that includes children. (see VHA Handbook 1200.05 Requirements for the Protection of Human Subjects Research).

Vertebrate Animals: Is the proposed involvement and protection of vertebrate animals appropriate and adequate? Is there an appropriate and adequate justification for the use of animal species and numbers proposed? Is the proposed veterinary care adequate? Are the procedures for limiting pain and distress which is unavoidable appropriate? Are the methods of euthanasia appropriate?

3. Disapproved Applications

An application may be disapproved if the SRG determines that the proposed studies are unethical.

- Disapproved applications are not given a numerical score and may not be resubmitted.
- Studies disapproved for ethical considerations may not be carried out in a VA space or with VA resources, even if the project is funded by another agency.

4. Appeals

CSRD will not accept Letters of Appeal for applications submitted to this RFA.

Section VI. Award Administration Information

1. Award Notices

After the application is peer reviewed, the PD/PI will be able to access the Summary Statement via the NIH eRA Commons site. If the application is under consideration for funding, VA-ORD will request "Just-in-Time" information from the applicant

2. Administrative and National Policy Requirements

Research Integrity: VA-ORD is committed to the highest standards for the ethical conduct of research. Maintaining these high ethical standards requires that VAMCs and investigators applying for (and receiving) Merit Review Awards have appropriate procedures to prevent unethical research practices.

As a condition of accepting the award, the PD/PI and others associated with the research must:

- Subscribe to accepted standards of rational experimental research design
- Accurately record data
- Conduct unbiased data reporting
- Respect the intellectual property of other investigators
- Adhere to established ethical codes and legal standards for protecting Human and Animal Subjects
- Properly manage research funds

Deliberate falsification or misrepresentation of research data will result in withdrawal of an application, possible suspension or termination of an award and, potentially, suspension of the investigator's eligibility to submit applications to VA-ORD.

Acknowledging VA Research Support: By accepting a Merit Review Award, the PD/PI agrees to properly acknowledge VA affiliation and support in all public reports and presentations (see VHA Directive 1200.19). **Failure to acknowledge VA affiliation and support may result in termination of the award.**

Intellectual Property Rights: By accepting a Merit Review Award, the PD/PI agrees to comply with VA policies regarding intellectual property disclosure obligations and Federal Government ownership rights resulting from the proposed work (see VHA Directive 1200.18).

Annual Reports: By accepting a Merit Review Award, the PD/PI agrees to complete an annual Federal-wide RPPR for the project. Information and instructions for RPPR can be found here: http://www.research.va.gov/resources/RPPR.cfm.

Section VII. Agency Contacts

We encourage scientific/programmatic inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

1. Scientific/Research Contacts:

To ensure a timely response prior to submission, all questions concerning electronic submission should be submitted by the appropriate R&D Office staff to the eRA mailbox: rd-era@va.gov.

If the initial assignment to an R&D Service or SRG seems inappropriate, the local R&D Office may request reassignment on behalf of the PD/PI.

Inquiries from the local R&D Office about the review process should be sent to vhacoblcsrdrev@va.gov.

Directly after funding decisions have been made, applicants may contact the appropriate Scientific Review Officer (SRO) with questions about issues raised in the Summary Statement. Click here for SRO contact information for individual SRGs.

For inquiries about clinical trials, applicants may send an email to CLIN-Review@va.gov