

Precision Oncology Actively Managed Portfolio

Guidance for Submission of a Letter of Intent for Accelerated Review Clinical Trial Award

I. Introduction

The application process for a Precision Oncology (PO) Actively Managed Portfolio (AMP) Clinical Trial begins with the preparation and submission of a Letter of Intent (LOI). **Please note that a clinical trial proposal may not be submitted without approval.** The primary purpose of the LOI is to provide PO AMP with the opportunity to determine if a proposed trial will address a critically important area in precision oncology, impact clinical practice and/or inform healthcare decision making and whether we would consider it for funding. In addition, submission of the LOI allows PO AMP to assess and provide feedback on the clinical focus and design of the trial; the innovation, overall impact, and translational potential of the proposed trial; and the apparent feasibility of enrolling the proposed Veteran population. If the proposed trial does not meet the PO AMP definition of a clinical trial (see Section II), a recommendation will be made that the applicant utilize a non-trial RFA. Similarly, if the proposed trial does not fall under the purview of PO AMP, a recommendation will be made that the proposed project be redirected to another research service and/or normal Merit review process.

II. PO AMP Clinical Trial Definition

Clinical trial means a 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 or behavioral health-related outcomes.

Proposals that meet the definition of a clinical trial and require an LOI typically involve:

- Randomization of human subjects and appropriate controls;
- Utilization of interventions including, but not limited to, pharmaceutical compounds, agents, treatments, or devices;
- Clinical outcome measure(s) to assess the potential safety and/or effectiveness of the intervention that are either direct or indirect measures of a surrogate endpoint (e.g., a validated biomarker) that are clinically meaningful;
- A study that does not have a primary clinical outcome measure, but in which safety is a major concern
- Studies planning to be submitted under any clinical trial RFA

Proposals that do not meet the definition of a clinical trial and do not require an approved LOI include:

- Proposals designed to show equivalence between new and existing diagnostic devices or methods;
- Studies that focus on mechanisms underlying an intervention (i.e., a mechanistic study) and which do not specify a clinical outcome measure as a primary focus;
- Studies that evaluate tests and/or procedures aimed at diagnosing diseases (i.e., a diagnostic study);
- Studies that do not have a primary clinical outcome measure of interest and that do not have any affiliated safety concerns;
- Observational, retrospective, and some prospective studies (e.g., a prospective study that has weight gain as the outcome and quantifies lifestyle habits as a risk factor)

Note: If you are uncertain as to whether or not an LOI is required for your study, please refer to the LOI decision tool or send an e-mail to CLIN-Review@va.gov. Applicants are encouraged to speak with the Senior Portfolio Manager for Precision Oncology prior to submitting an LOI.

III. Definition/Purpose of RFA

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.

Applications 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. 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.

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

IV. LOI Approval Considerations

The following areas must be detailed in your LOI:

A. Focus:

A PO AMP clinical trial LOI must:

1. Address a critically important cancer problem that is unique to the Veteran population, or an individually tailored treatment that will examine the direct improvement of the healthcare of Veterans;
2. Constitute the sole objective of the application; thus, a clinical trial cannot be proposed as one of several specific aims of an application.

B. Design

A clinical trial LOI submitted to the PO AMP accelerated review funding mechanism must include and describe:

1. An appropriate study design statistically powered with a sufficient sample size to determine the effect of the proposed intervention;
2. A clinically meaningful outcome measure;
3. A method of reducing or controlling bias (randomization and masking/blinding) to allow for a meaningful interpretation of the results;
4. Appropriate control groups;
5. Rationale for the significance tests to be used;
6. Sufficient evidence supporting the feasibility of enrolling the target Veteran population;
7. Plan for managing multiple sites based on performance metrics. If a PI proposes a recruitment site that does not have a strong performance record for recruiting, a detailed mentoring plan should be provided in the full application.

8. Describe all phases proposed, e.g., if submitting to staged trial with interim analysis

V. Components of the LOI Submission

Each LOI submission must contain the three following required components:

1. **VHA Research and Development Letter of Intent Cover Page (VA Form 10-1313-13)**

This form is available on the forms page of the [VA Research website](#).

2. **Completed LOI template for Precision Oncology AMP accelerated review**

The template to apply for an accelerated review for the Precision Oncology AMP can be found at https://www.research.va.gov/services/shared_docs/resources.cfm.

3. **Primary Investigator Biographical Sketch**

The biographical sketch template is available on the VA Research Intranet. If you cannot access the intranet, please contact your local research office. **Note:** The biosketch of all local site investigators must be attached. If a multi-site clinical trial is being proposed, all local site investigators' biosketches must be included also.

VI. Submission of the LOI

The LOI will be reviewed and the outcome (i.e., approval or disapproval) of the review will be sent to the local Research Office. An LOI for accelerated review must be submitted before the posted deadline in order for the project to be considered for review at the next quarterly SMRB meeting. LOIs must be e-mailed mailed by the local Research Office to CLIN-Review@va.gov. Applicants may not upload LOIs directly to the mailbox. Questions relating to the LOI for accelerated review preparation and submission process may also be directed to the Senior Portfolio Manager for Precision Oncology. **Applicants are strongly encouraged to submit LOIs as early as possible.**

LOIs with the following issues will be withdrawn:

- a. Multiple submissions on behalf of the same PI,
- b. LOIs lacking the requisite information (i.e., incomplete),
- c. LOIs submitted for deadlines that have already passed,
- d. LOIs submitted by investigators that are ineligible to receive VA funding.

LOIs meeting all of the administrative requirements are subject to rejection if the proposed research:

- a. Does not fall within the purview of the Precision Oncology,
- b. Does not meet the threshold for an accelerated review for a clinical trial,

- c. Lacks innovation and/or impact,
- d. Does not address a medical issue related to precision oncology faced by the Veteran population,
- e. Is overly represented by ongoing ORD-funded clinical trials.

VII. Approval

The LOI approval letter must be submitted with the full application package (in the Letters of Support attachment). **A submitted clinical trial application must not deviate significantly in specific aims from the original approved clinical trial LOI. PO An application may be administratively withdrawn from review if it substantially deviates from what was described and approved at the LOI submission stage.**

An approved clinical trial LOI for PO AMP is valid for a maximum of two (2) submissions of an application (initial submission and one resubmission) during a period that encompasses two (2) consecutive review cycles following the initial approval of the LOI.