

## Guidance for Submission of a Letter of Intent for a Clinical Trial Merit Award

### I. Introduction

The application process for a CSR&D Merit Review 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 an approved LOI.** *The primary purpose of the LOI is to provide CSR&D with the opportunity to determine if a proposed trial will address a critically important disease that is prevalent in the Veteran population.* In addition, submission of the LOI allows CSR&D 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 CSR&D 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 research purview of CSR&D, a recommendation will be made that the proposed project be redirected to a research service other than CSR&D.

### II. CSR&D Clinical Trial Definition

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

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);
- 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:* The criteria that define the requirement for an LOI for a CSR&D trial might be stricter than the requirements for a trial to be registered on clinicaltrials.gov: [http://www.research.va.gov/resources/ORD\\_Admin/clinical\\_trials/](http://www.research.va.gov/resources/ORD_Admin/clinical_trials/). 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](mailto:CLIN-Review@va.gov). Applicants are encouraged to speak with their [Portfolio Manager](#) prior to submitting an LOI.

### **III. LOI Approval Considerations**

The following areas must be detailed in your LOI:

#### **A. Focus:**

A CSR&D clinical trial LOI must:

1. Address a critically important disease 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 CSR&D Merit 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.

### **IV. Components of the LOI Submission**

LOIs must be submitted using the following template. Each LOI must contain the following three required components (A-C):

#### **A. VHA Research & Development Letter of Intent Cover Page (VA Form 10-1313-13)**

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

#### **B. Completed LOI Template**

The template is available on the CSR&D [webpage \(Section IV, 3\)](#).

### **C. PI's 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. Please indicate specific clinical trials experience by highlighting work in the biosketch. **Note:** If you are proposing a multi-site clinical trial, the biosketch of all local site investigators must be attached.

**D. The following addenda** should be submitted with the LOI (if necessary):

#### **a. Waiver request to approve an early phase trial**

In extremely rare circumstances, the CSR&D Director may approve an LOI for an early phase trial (e.g., studies examining first use in humans, safety, or dosing), provided safety data is available in at least two animal species. Early phase (Phase 0 and Phase 1) studies present particular challenges that Phase 2–4 trials do not present in terms of subject safety. Sufficient safety data should be presented as part of the LOI in order to justify approval because these studies are high risk projects that involve an unknown propensity for research-related injuries. Investigators proposing such studies must demonstrate that they and their study teams are experts in the particular subject area. This waiver request should be described in a memorandum; addressed to the Director, CSR&D; signed by the ACOS/R; and submitted as an addendum to the LOI. Enrollment of non-Veterans may not be proposed in early phase trials.

#### **b. Waiver to exceed the Merit Review budget cap**

Rare exceptions to the budget cap may be granted prior to application submission for fully justified and compelling circumstances, especially with the higher budget cap effective as of the Fall 2018 application round. A detailed justification must be included in a written request for this waiver. Waiver requests must be submitted as an addendum to the LOI by the local Research & Development Office, and signed by the ACOS/R. For instructions on preparing/submitting a waiver request, refer to the document entitled "[Instructions for Preparing and Submitting a Waiver to Exceed Budget Caps](#)."

#### **c. Waiver request for enrollment of non-Veteran subjects**

Enrollment in CSR&D trials is limited to Veterans, unless a waiver to enroll non-Veterans is approved by the CSR&D Director. The request for a non-Veteran enrollment waiver should be submitted as an addendum to the LOI and should provide sufficient justification for enrollment of non-Veterans and still support the relevance of the trial to the Veteran population. These requests are highly scrutinized. FAQs and waiver template can be accessed on the [CSR&D website](#).

#### **d. FDA Documentation**

If the proposed trial will require an Investigational New Drug (IND) or Investigational Device Exemption (IDE) with the FDA, documentation of status of IND/IDE application should be included with the LOI.

#### **e. Availability/Access Documentation**

Attach documentation of availability and access to pharmaceutical compounds or agents, biologics, treatments, or devices. *Note:* the quality of the agent/product should be consistent with FDA manufacturing standards.

#### **V. Submission of the LOI**

CSR&D will review and respond to submitted LOIs at any time; however, an LOI must be submitted no later than **November 1** for proposals intended for submission to the Spring Merit Review cycle, and **no later than June 1, 2018 (for this one round only)** for proposals intended for submission to the Fall Merit Review cycle. LOIs must be e-mailed to [CLIN-Review@va.gov](mailto:CLIN-Review@va.gov) by the local VA facility research office. Applicants may not upload LOIs directly to the mailbox. Questions relating to the LOI preparation and submission process may also be directed to [CLIN-Review@va.gov](mailto:CLIN-Review@va.gov). **Applicants are strongly encouraged to submit LOIs as early as possible.**

LOIs with the following issues will be administratively withdrawn:

- Multiple submissions on behalf of the same PI;
- LOIs lacking the requisite information;
- LOIs submitted by investigators who are not eligible to receive VA funding.

LOIs meeting all of the administrative requirements will be reviewed on the following criteria:

- Innovation/impact that addresses a clinically relevant disease prevalent in the Veteran population;
- Falls within the purview of CSR&D and/or research priority area;
- Are not overly represented by ongoing funded clinical trials;
- Feasibility of recruitment at proposed site(s).

#### **VI. Approval**

The LOI approval letter must be submitted with the full application package (in the Letters of Support attachment, 08b\_VA\_Letters.pdf). **A submitted clinical trial application must not deviate significantly in specific aims from the original approved clinical trial LOI. CSR&D may administratively withdraw from review any application that substantially deviates from what was described and approved at the LOI stage.**

An approved clinical trial LOI is valid for a maximum of three (3) submissions of an application (initial submission and up to two resubmissions) during a period that encompasses four (4) **consecutive** review cycles following the initial approval of the LOI.

Effective: April 20, 2018