Clinical Science Research & Development (CSR&D)

Guidance for Merit Review Clinical Trials: Letter of Intent (LOI)

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 full 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, or is an individually tailored treatment that will directly improve the healthcare of Veterans**. In addition, submission of the LOI allows CSR&D to assess and provide feedback on the clinical focus and design of the trial, the proposed innovation and 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, a recommendation will be made that the applicant utilizes 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 (e.g., Health Services Research and Development).

II. Determining if an LOI is Needed

In CSR&D, a clinical trial application that ***requires*** an approved LOI typically involves:

- Randomization of human subjects and appropriate controls;
- Utilization of interventions including, but not limited to, pharmaceutical compounds, agents, treatments or devices;
- Clinical outcome(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);
- A study that does not have a primary clinical outcome measure, but in which safety is a major concern

In CSR&D, a clinical trial application that ***does not*** require an approved LOI includes:

- 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/. 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.

III. LOI Approval Considerations

The following areas must be detailed in your LOI.

A. Focus:

A clinical trial LOI submitted to the CSR&D Merit Review funding mechanism must:

a. Address a critically important disease that is unique to the Veteran population, or an individually tailored treatment that will directly improve the healthcare of Veterans;

   i. The disease or condition should also have a well characterized etiology with outcome variables that do not vary;

b. 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:

a. Include an appropriate study design with a sufficient sample size (n) and statistical power to determine the effect of the proposed intervention;

b. Include a method of reducing or controlling bias (randomization and masking/blinding) to allow for a meaningful interpretation of the results;

c. Include appropriate control groups;

d. Include measurable outcomes that are responsive to change;

e. Describe in sufficient detail the significance tests to be used;

f. Demonstrate with sufficient evidence the feasibility of enrolling the target Veteran population.

III. Components of the LOI Submission

LOIs must be prepared using only letter-quality print, and all text must be prepared using at least 11-point font, with no more than 15 characters per inch and no more than 6 lines per inch. Page margins must be a minimum of 1 inch at each edge. Each LOI must contain the following materials:

A. VHA Research & Development Letter of Intent Cover Page (VA Form 10-1313-13) (http://www.research.va.gov/funding/process/forms.cfm)

B. LOI Text – Limited to three (3) pages. Please clearly and succinctly address **ALL** of the following requirements in the specified order:

I. Subjects, Sample Size, and Feasibility

1. Proposed number of subjects = _____
2. Number of sites = _____
3. Duration = _____ years
4. Description of the study category using FDA Phase Definitions (e.g., Phase 0, 1, 2, 3, or 4; http://clinicaltrials.gov/ct2/help/glossary/phase)
5. Sample size determination including a power analysis to justify the number of subjects. Describe the assumptions for sample size including effect size, event rates, or mean differences with standard deviations and expected drop-out rates. Specify the statistical methods used to calculate sample size.
6. Brief description of subject screening/recruitment methods and inclusion/exclusion criteria.
7. Projected recruitment rate.
8. As evidence of feasibility, data describing the size of the subject population available at the recruiting site(s) and verification of access to the appropriate Veteran population must be provided.
9. A list of any local or national competing trials on this topic that would draw subjects from the same Veteran population must be included. If competing trials exist, the distinction from the proposed trial must be accurately described. If no competing trials are underway, indicate NONE. See www.clinicaltrials.gov as one source for this information.

II. Study Outline and Statistical Methods

1. Brief description of the objectives of the proposed clinical trial and the hypothesis to be tested
2. Description of the primary endpoint

3. Description of proposed intervention and control/s
4. Scientific Rationale and Significance to the Veteran population
5. Background Data/Preliminary Studies conducted to support application
6. Study Design/Methods
7. Data Analysis Plan
8. Description of how the results will impact clinical practice and/or plans for further studies
9. Description of any anticipated problems or challenges regarding timely start up and execution (including whether the study will be FDA regulated, agreements with industry or other non-VA entity, patents/licensing, etc.). *Note*: If the proposed trial will require an Investigational New Drug (IND) or Device Exemption (IDE), approval from the Food and Drug Administration must be obtained prior to submission of the LOI, and a copy of the IND/IDE documentation provided.

III. Budget

1. Total study budget and approximate breakdown of funds to be requested each year.

C. **Supplemental Pages:**

1. PI's Biographical Sketch. Attach completed form listed under "Additional Format Pages", Biographical Sketch Format Page: http://vaww.research.va.gov/funding/electronic-submission.cfm Please highlight specific clinical trials experience. A proven track record of conducting clinical trials is a prerequisite for approval of an LOI.
2. Documented availability of and access to pharmaceutical compounds or agent, biologic, treatments or devices. *Note*: the quality of the agent/product should be consistent with FDA manufacturing standards.

D. **Addenda** (If necessary)

1. Waiver request to approve an early phase trial; please refer to Section VI (1).
2. Waiver to Exceed the Merit Review Budget Cap; please refer to Section VI (2).
3. Waiver request for enrollment of non-Veteran subjects; please refer to Section VI (3).

IV. Submission of an LOI

CSR&D will review and respond to submitted LOIs at any time; however, an LOI must be submitted no later than **November 1st** for proposals intended for submission to the Spring Merit review cycle, and **May 1st** for proposals intended for submission to the Fall Merit review cycle. LOIs must be e-mailed to 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.

Applicants are strongly encouraged to submit LOIs as early as possible. A Principal Investigator may only submit one LOI per review cycle. Multiple submissions on behalf of the same PI will be administratively withdrawn. Only complete LOI submissions that include all of the required information will be reviewed. Any LOI lacking the requisite information will likewise be administratively withdrawn.

Note: LOIs meeting all of the administrative requirements but a) lacking innovation/impact or that do not address a clinically relevant disease prevalent in the Veteran population; b) that do not fall within CSR&D purview and/or a research priority area; c) are overly represented by on-going ORD funded clinical trials; d) describe clinical trials that are not subject to an approved LOI (e.g., diagnostic or mechanistic studies); or e) LOIs submitted by investigators that are not eligible to receive VA funding are likewise subject to disapproval.

V. Approval

If an LOI for a clinical trial is approved, the LOI approval letter must be submitted with the full application package (in Letters attachment). **A submitted clinical trial application must not deviate 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.

VI. Special Considerations

1. **Waiver for Early Phase Trials:** 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. Enrollment of non-Veterans may not be proposed in early phase trials. 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.
2. **Waiver to Exceed the Merit Review Budget Cap:** Rare exceptions to the budget cap and/or maximum study duration may be granted prior to application submission for fully justified and compelling circumstances. A detailed

justification must be included in a written request for a waiver. Waiver requests must be submitted to vhacoblcsrdrev@va.gov 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" available at: http://www.research.va.gov/services/shared_docs/merit_review_guidance_docs/loi-budget-caps.doc.

3. **Waiver for Enrolling Non-Veterans:** 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. This waiver request should be described in a memorandum, addressed to the Director, CSR&D, signed by the ACOS/R, and should provide sufficient justification for the enrollment of non-Veterans and still support relevance of the trial to the Veteran population.

Effective: October 15, 2015