

STANDARD OPERATING PROCEDURES FOR PHASE I, II, III AND IV CLINICAL TRIAL COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS

Purpose:

This document establishes procedures to be followed by VA Medical Centers (VAMCs) and VA Nonprofit Corporations (NPCs) when negotiating and executing clinical trial Cooperative Research and Development Agreements (CT CRADAs).

NOTE: Where there is no NPC, VAMC is responsible for tasks assigned to NPCs in these Standard Operating Procedures.

Scope:

CT CRADAs shall be used when a VAMC is interested in participating in a study for which a commercial company 1) owns the investigational new drug (IND); 2) designs the protocol; **and** 3) funds the project.

For model CRADAs suitable for other circumstances, such as basic research or the transfer of material only, please contact Technology Transfer Program staff.

Responsibility: Technology Transfer Program (TTP) Staff

General Information:

The Investigator, the Associate Chief of Staff for Research (ACOS), Administrative Office for Research (AO), NPC, and Regional Counsel (RC), as needed, negotiate with the Collaborator the terms of the CT CRADA based on the VA approved model available on the TTP **intranet** website at http://vaww.research.va.gov/programs/tech_transfer/model_agreements/default.cfm. After negotiations are complete, the CT CRADA must be submitted to RC for legal review and approval with changes to the model, if any, shown in tracked changes mode.

If RC determines that terms negotiated in the CT CRADA differ significantly from those in the model, RC will forward the agreement to TTP for review and approval with cc's to the Office of General Counsel (OGC), Professional Staff Group III (023) and to the NPC. TTP will coordinate with OGC (023) for legal review of those clauses. OGC will respond directly to TTP with comments. Insignificant wording changes the sponsor requests for clarity (wordsmithing) or to meet the sponsor's own needs are permissible and do not need to be sent to TTP.

For purposes of formally tracking CRADAs and creating an educational resource, VAMCs or NPCs are required to register CT CRADAs through the TTP Internet website at http://www.research.va.gov/programs/tech_transfer/crada/resources.cfm when they begin negotiations and again after executing a signed CRADA.

If the CRADA involves a foreign corporation or government, NPC should notify TTP as soon as possible in order for TTP to initiate clearing the CRADA through the U.S. Trade Representative. Send an email to Noahline.stuart@e2k.va.gov providing 1) the title of the study; 2) the name of the company; and 3) the country where the company is doing business. A CRADA with a U.S. subsidiary of a foreign company does not need clearance through the U.S. Trade Representative.

Procedures for negotiating and entering into a CT CRADA:

1. Consistent with local policies and procedures, investigator informs the ACOS, AO or the Coordinator for Research and Development (R&D) and the VA NPC affiliated with the VAMC of interest in participating in an industry-sponsored clinical trial.
2. No CT CRADA involving an investigator who is a dually appointed personnel (DAP) holding both a VA and an academic affiliate position may be entered into unless either 1) the applicable Cooperative Technology Administration Agreement provides that VA will take the lead on patenting, marketing, and licensing any invention made under the CT CRADA; or 2) VA and the university agree on a case-by-case basis to VA taking the lead on managing CRADA subject inventions. NPC personnel will confirm any necessary university approvals prior to entering into a CT CRADA involving a DAP.
3. Investigator completes a Conflict of Interest survey (see link below).
4. Consistent with local policies and procedures, appropriate VA Research Service staff or the NPC informs the Medical Center Director that a CT CRADA is being developed.
5. To initiate development of a CT CRADA for a project, NPC personnel provide the Collaborator with a copy of the most recent version of the appropriate model CT CRADA downloaded from the TTP **intranet** website at http://vaww.research.va.gov/programs/tech_transfer/model_agreements/default.cfm and with the involvement of RC as needed, negotiate terms to arrive at a proposed CT CRADA acceptable to the Collaborator and ready for submission to RC. Involving RC in negotiations where the Collaborator's legal counsel is involved is highly recommended.
6. Prior to initiating negotiations, NPC should check the CRADA registry to determine if a similar study has already been negotiated with another VAMC. If the same study is listed on the registry, the NPC should contact the other facility to ensure consistency in the agreements and expedite negotiations.

7. Upon initiating negotiations for CT CRADAs, NPC should complete the CRADA registry Excel spreadsheet at http://www.research.va.gov/programs/tech_transfer/crada/resources.cfm to the extent possible and send it to TTP (Noahline.stuart@e2k.va.gov) via e-mail. The information provided will be integrated into the master Excel registry and posted on the TTP Internet website.
8. Upon completion of negotiations with the Collaborator, NPC forwards an electronic copy of the proposed CT CRADA showing tracked changes and the Conflict of Interest survey to the RC for review and approval.
9. In addition, NPC forwards to the RC a draft memo (the “justification memo”) from the Regional Counsel to the Director of the VAMC or local equivalent that:
 - a. states that there are no changes that are believed to be “significant,” that the RC concurs in the proposed CRADA and recommends that the Director sign it, or
 - b. identifies changes that are believed to be “significant” and contains justification for the approval of the significant changes identified, including an explanation of the factors deemed to be important in the particular case, or
 - c. identifies changes that are believed to be significant and contains a statement that the proposed CRADA represents a best effort, although it contains significant variation for which there is not available justification. See Guidance below.
10. Regional Counsel then:
 - a. forwards the proposed CRADA found by the RC not to contain significant changes to the VAMC Director for signature, together with a final of the justification memo, concurring in the CRADA; or
 - b. forwards a tracked-changes electronic version of a proposed CRADA found by the RC to contain significant changes from the model, together with the justification memo, to the Director, TTP (12TT), for review, with a copy to OGC (023) and to the NPC. TTP will coordinate with OGC (023) for legal review and comments.
11. In any case in which the proper documents are provided, the RC will complete its review in 10 working days or less. Where the documentation requires additional work, or is particularly complicated, the RC will complete its review and move the CRADA on in no more than 20 working days.

12. TTP will respond to the RC, with comments from Central Office, with a copy to 023 and the NPC, within 15 working days of TTP's receipt of the proposed CRADA with significant changes, indicating approval, disapproval or recommended changes, and suggesting next steps.
13. After the CT CRADA is approved, the NPC will prepare a sufficient number of originals (one for each party) for signature. Each original must be signed by:
 - an authorized representative of the Collaborator;
 - an authorized representative of the NPC when applicable;
 - the Principal Investigator; and lastly
 - the Medical Center Director.
14. The NPC will distribute the executed CT CRADA and copies thereof as follows:
 - One original to each signatory of the CT CRADA;
 - Copies to Director TTP, ACOS and RC.
15. As soon as CT CRADAs are executed, NPC must add the remaining information to the Excel spreadsheet and re-send it to TTP. If negotiations terminate without an executed CRADA, the NPC should notify the TTP office and it will be noted on the CRADA Registry.
16. The total amount of CT CRADA funds (broken down per CT CRADA) received by a specific VAMC/NPC during the previous twelve months from October 1 through the following September 30 shall be reported to TTP every October.

Conflict of Interest Considerations:

The Conflict of Interest (COI) survey is available at the TTP website:
http://www.research.va.gov/programs/tech_transfer/model_agreements/conflict.doc

VA requirements regarding employee conduct standards in general and the avoidance of conflict of interest in particular are contained in 5 C.F.R. §735. Conflict of Interest laws are criminal statutes and are found in title 18 of the United States Code. In order to comply with these statutes and regulations and the Federal Technology Transfer Act, any potential conflict identified in the conflict of interest survey or arising during the negotiation and conduct of a CRADA or in the commercialization of inventions resulting from a CRADA should be immediately discussed with RC.

A copy of the COI survey must be provided to RC with the CT CRADA submission. The original must be maintained in the CT CRADA file at the VAMC.

Guidance for the Justification Memo:

Justification for Significant Changes: The factors that should be weighed in a particular case include, but are not limited to:

- The VAMC's view of the importance to veterans and VA of the research based on its subject matter;
- The ownership of substantial background inventions by the Collaborator;
- The extent to which the research involves substantial VA resources (personnel, equipment, etc.) or a substantial intellectual contribution to the research by VA;
- The relevance of the research to a PI's other or ongoing research;
- Availability of alternative treatments for veterans;
- The VAMC's view of the likelihood that new IP may arise in the course of the research (the "IP risk");
- RC's view that the changes, although numerous, do not make a meaningful significant change in the import of the provision.

Significant Changes: Changes to any one of the following subject areas within the Model Phase I, II, III and IV CT CRADA that are beyond stylistic are likely to be significant because of the sensitivity of their substance. They should be carefully considered to determine their nature as significant or not.

- **Definitions** (Article 2)
- **Data rights and ownership** (see § 3.2 Use and disposition of Collaborator Materials, §7.1 Case Report Forms and Records, § 7.2 CRADA Data and CRADA Materials)
- **Pre-commitment of IP rights in CRADA Subject Inventions** (see §5.2 Ownership of CRADA subject inventions)
- **Licensing** (see Article 6)
- **Privacy rights of veterans** (see §§7.1 and 7.2)
- **Indemnification by VA and costs of subject injury** (see §§12.2 and 12.3)

Minor Additions – Additions that clarify details or improve the administration of the CRADA may be added as desired by the parties. Such additions will not be considered significant variations and do not require justification. They include the following:

- A requirement to report or list Background Inventions in an attachment or elsewhere
- A requirement to identify Collaborator or VA materials or Collaborator Capital Equipment under the CRADA;

- A prompt for addition of NPC's Tax ID number or a payment schedule, or attachment of a budget spreadsheet.

REFERENCES

VHA Handbook 1200.18

FOLLOW UP DATE

June 2009