

VAMHCS HUMAN RESEARCH PROTECTION
STANDARD OPERATING PROCEDURE

SOP# HRP 01.15

Approval Date: 5/8/08

NEGOTIATING AND ENTERING INTO A PHASE I, II, III AND IV CLINICAL
TRIAL COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS
(CRADA)

OBJECTIVES:

- To establish procedures to be followed by the VA Maryland Health Care System (VAMHCS) and the Baltimore Research and Education Foundation (BREF) when negotiating and executing clinical trial Cooperative Research and Development Agreements (CT CRADAs).
- To ensure that the VAMHCS has a written agreement with the sponsor of each research project that delineates the responsibilities and obligations that the VAMHCS will fulfill for the Sponsor and that the Sponsor will fulfill for the VAMHCS.
- To ensure that the VAMHCS and the Sponsor agree to specified actions that protect research participants, including: medical care for research participants with a research-related injury, reporting of findings that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study, the publication or disclosure of results, and reporting of study results to participants.
- To protect intellectual property rights due to the VA through work done or data obtained through research projects conducted in VA sites or by VA investigators.

POLICY:

The VAMHCS negotiates and executes CT CRADAs for all sponsored research in which: 1) there is an issue of pre-assignment of intellectual property rights, and 2) the sponsor owns the investigational new drug or device, 3) designs the protocol; **and** 4) funds the project.

BACKGROUND AND SCOPE:

The VAMHCS conducts clinical research funded by various sponsors. As of 3/26/08, the VA requires that a CT CRADA be used for all sponsored research: 1) that requires pre-assignment of intellectual property rights, and 2) the sponsor owns the investigational new drug or device, 3) designs the protocol; **and** 4) funds the project.

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The Investigator, the Associate Chief of Staff for Research (ACOS), Administrative Officer for Research (AO), BREF, and Regional Counsel (RC), as needed, negotiate with the Sponsor the terms of the CT CRADA based on the VA approved model available on the TTP **intranet** website at http://vawww.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 BREF. 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, the VAMHCS / BREF 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, the BREF 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@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.

DEFINITIONS

Baltimore Research and Education Foundation (BREF) – the VAMHCS-affiliated non-profit research and education corporation (NPC) created and operated under the laws of the State of Maryland. The NPC's role and obligations are set forth in the CRADA pursuant to its statutory authority under 38 U.S.C. §§ 7361-68 and VHA Handbook 1200.17.

Cooperative Research and Development Agreements (CRADA) - Established under the Federal Technology Transfer Act of 1986, Public Law (Pub. L.) 99-502, CRADAs were created to serve as a flexible form of agreement between Federal and non-Federal organizations for establishing the terms of collaborative research efforts. CRADAs were specifically designed to respect both government and non-government organizations' rights to intellectual property in order to foster

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translation of research results into commercial products. CRADAs, which are legally binding on all parties, allow the Department of Veterans Affairs (VA) to establish ownership and licensing rights to inventions in advance. A template is available at the VA Technology Transfer Program intranet site.

Technology Transfer Program (TTP) - The mission of the VA Technology Transfer Program (TTP) is to serve the American public by translating the results of worthy discoveries made by employees of VA into practice. This requires a program that educates inventors concerning their rights and obligations, rigorously evaluates all inventions, obtains patents, and assists in the commercialization of new products. It also requires consistent policies that govern the necessary relationships between investigator (i.e., inventor), academic partners, local VA medical centers, industry, and the Department of Commerce. It requires close collaboration between ORD and the VA Office of General Counsel (OGC).

RESPONSIBILITIES

ACOS for R&D, Deputy ACOS, AO/ R&D and/or Executive Director (ED) of BREF

- When notified by an investigator of intentions to participate in a clinical trial, decides whether CRADA requirements apply;
- Negotiates with Sponsor the terms of Clinical Trial CT CRADAs.

Principal Investigator

- Is responsible for notifying the ACOS, Deputy ACOS, AO/R&D, and/or ED of BREF when s/he has decided to participate in a clinical trial conducted by a Sponsor.

VAMHCS Regional Counsel (RC)

- May assist in negotiation of CRADA with sponsor.
- Performs legal review and approval with changes to the model (if any) shown in tracked changes mode.

PROCEDURES:

1. At the time that an investigator decides to initiate or participate in an industry-sponsored clinical trial s/he informs the ACOS, Deputy ACOS, AO/ACOS and/or and the Executive Director of BREF prior to entering into negotiations with the Sponsor.
2. No CT CRADA involving an investigator who is a dually appointed personnel (DAP) holding both a VAMHCS a University of Maryland position may be entered into unless either 1) the applicable Cooperative Technology

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Administration Agreement provides that VA will take the lead on patenting, marketing, and licensing any invention made under the CT CRADA; or 2) VAMHCS and the University agree on a case-by-case basis to VA taking the lead on managing CRADA subject inventions. BREF personnel will confirm any necessary university approvals prior to entering into a CT CRADA involving a DAP.

3. The investigator completes a Conflict of Interest survey (see #17 below).
4. To initiate development of a CT CRADA for a project, BREF personnel provide the Sponso 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/techtransfer/model_agreements/default.cfm With the involvement of Regional Counsel, as needed, they negotiate terms to arrive at a proposed CT CRADA acceptable to the Sponsor and ready for submission to RC. Involving RC in negotiations where the Sponsor's legal counsel is involved is highly recommended. The CRADA template ensures that:
 - 4.1. there is an agreement that the organization will follow the protocol and applicable law;
 - 4.2. there is an agreement on who would provide care and who is responsible to pay for the care;
 - 4.3. there is an agreement that obligates the sponsor to promptly report to the VAMHCS any findings that could:
 - 4.3.1. Affect the safety of participants,
 - 4.3.2. Affect the willingness of participants to continue participation,
 - 4.3.3. Influence the conduct of the study,
 - 4.3.4. Alter the IRB's approval to continue the study.
 - 4.4. there is an agreement that obligates the sponsor to follow the DVA's policies and procedures regarding the publication of findings from sponsored research
 - 4.5. there is an agreement on how results from a research study will be communicated to participants when those results directly affected their safety or medical care.
5. Prior to initiating negotiations, BREF 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 BREF should contact the other facility to ensure consistency in the agreements and expedite negotiations.
6. Upon initiating negotiations for CT CRADAs, BREF should complete the CRADA registry Excel spreadsheet at <http://www.research.va.gov/programs/techtransfer/crada/resources.cfm> to the extent possible and send it to TTP (Noahline.stuart@va.gov) via e-mail. The information provided will be integrated into the master Excel registry and posted on the TTP Internet website.

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7. Upon completion of negotiations with the Sponsor, BREF 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.
8. In addition, BREF forwards to the RC a draft memo (the "justification memo") from the Regional Counsel to the Director of the VAMC or local equivalent that:
 - 8.1. 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
 - 8.2. 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
 - 8.3. 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.
9. Regional Counsel then:
 - 9.1. forwards the proposed CRADA found by the RC not to contain significant changes to the MCD for signature, together with a final of the justification memo, concurring in the CRADA; or
 - 9.2. forwards a tracked-changes electronic version of a proposed CRADA found by the RC to contain significant changes from the model CRADA, together with the justification memo, to the Director, TTP (12TT), for review, with a copy to OGC (023) and to the BREF. TTP will coordinate with OGC (023) for legal review and comments.
10. 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.
11. TTP will respond to the RC, with comments from Central Office, with a copy to 023 and the BREF, 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.
12. After the CT CRADA is approved, the BREF will prepare a sufficient number of originals (one for each party) for signature. Each original must be signed by:
 - an authorized representative of the Sponsor;
 - an authorized representative of the BREF when applicable;
 - the Principal Investigator; and lastly

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- the Medical Center Director.
13. The BREF will distribute the executed CT CRADA and copies thereof as follows:
- Copies to Director TTP, ACOS and RC
 - One original to each signatory of the CT CRADA.
15. As soon as CT CRADAs are executed, BREF must add the remaining information to the Excel spreadsheet and re-send it to TTP. If negotiations terminate without an executed CRADA, the BREF 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 the VAMHCS/BREF during the previous twelve months from October 1 through the following September 30 shall be reported to TTP every October.
17. Conflict of Interest:
- 17.1 The Conflict of Interest (COI) survey is available at the TTP website: http://www.research.va.gov/programs/tech_transfer/model_agreements/conflict.doc.
- 17.2 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.
- 17.3 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 VAMHCS.
18. Notification and role of the IRB
- 18.1 The ACOS or designee communicates to the IRB Director of Operations when a CRADA is in effect for a research project involving pre-assignment of intellectual property, thereby alerting the IRB to potential institutional financial interest in the project.
- 18.2 The IRB has final authority to determine whether the research is approvable.

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VHA Directive 2007-044 Use of a Cooperative Research and Development Agreement (CRADA) (December 26, 2007)

APPROVAL:

This SOP entitled “Negotiating and Entering into a PHASE I, II, III AND IV Clinical Trial Cooperative Research and Development Agreements (CRADA)” has been approved by the Medical Center Director, effective 5/8/08.

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