Guidance on Selection of the Appropriate CRADA Model

VA has created templates to stream-line entering into research agreements. Although the information contained within this guidance cannot address every question concerning selection of the appropriate CRADA model, the information will provide appropriate insight to the majority of questions. If two templates appear to be equally applicable, consider the need for terms related to human subject protections or privacy issues. It is easier to remove this language than to add it into an incorrect model. If you have further questions about the selection of the appropriate model please contact your TTP and OGC point of contact for further guidance.

You should always review the protocol or research plan available and, if necessary, consult with the PI and/or study coordinator before selecting the CRADA Model. To facilitate the selection of the appropriate CRADA model, you should consider the following:

a) Does the study involve human subjects? Will the collaborator receive materials derived from humans? If yes, then you should consider the following models:
   i. PI Initiated Phase 1/2, Phase 3/4, or Investigational Device.
b) Is the collaborator providing a proprietary drug that is subject to FDA oversight? If yes, then consider the following models:
   i. PI Initiated, Phase 1/2, or Phase 3/4 CRADAs (for clinical studies)
   ii. Basic CRADA, only if the proprietary drug is being used in non-clinical (no human subjects, no materials derived from humans) research
c) Is the collaborator providing a device that is subject to FDA oversight? If yes, then consider the following models:
   i. Investigational Device CRADA (when human subjects are involved)
   ii. If the equipment/device is not subject to FDA oversight then consider a Basic CRADA (which is for non-clinical studies)
d) Did the VA investigator write the protocol or research plan? If yes, consider the following models:
   i. PI Initiated
   ii. Basic CRADA (research does not involve human subjects) or
   iii. Data Use Agreement
e) Are the collaborator and VA entering into basic research with no human subject interactions? Animal studies may be involved.
   i. Basic CRADA
f) If no funding is being provided by the collaborator, the research is non-clinical, and materials such as animal models are being sent or received by the collaborator, consider the Material Transfer Agreement. The Material Transfer Agreement should not contain intellectual property or licensing terms. Use a Material Transfer CRADA if there are intellectual property or licensing terms and/or funds being exchanged.

Below is a synopsis of each CRADA model.

1. **Basic CRADA**

   This CRADA model is used for basic collaborative research and development, software, engineering, testing or evaluation studies in which the VA's Principal Investigator (PI) developed or substantially contributed to the research plan. Animal studies may be conducted under a Basic CRADA.

When to use the Basic CRADA model:

This CRADA is only used for non-clinical studies. The research does not involve human subjects and specimens derived from humans are not being provided to the collaborator. The VA PI designs or substantially contributes to the design of the research project. The study may involve creating an animal model for diabetes testing, or the testing or use of equipment. Examples of such research equipment are chromatography columns or microscopes.

2. Principal Investigator Initiated CRADA (PII)

The PII CRADA is for clinical research with a drug that is subject to FDA oversight in which the VA investigator has developed the protocol.

When to use the PII CRADA model:

The PII CRADA model should only be used for a clinical study with a human subject drug and/ or materials derived from humans and only when the VA PI has substantially designed the protocol. The VA *may* hold an investigational new drug (IND) application for drug. In this case the VA PI is both the trial Sponsor and the Sponsor-Investigator for the trial. In most instances, PII studies involve an FDA approved drug that is already on the market. However, there are times in which the PI develops a protocol for an experimental drug which will be provided by the collaborator.

Some involvement by the collaborator in the development of the protocol is permitted. If both the VA and collaborator have contributed to the design of the study, you identify who is the trial Sponsor. (see above). If the collaborator is the Sponsor then consider the Phase 1/ 2 or Phase 3/ 4 Clinical CRADA model.

3. Phase 1/2 Clinical CRADA

Definition: Phase 1- This phase is generally used to determine pharmacologic actions, how a drug is metabolized in humans, and the side effects associated with increasing doses. These trials are focused on safety aspects of an investigational product, although some early evidence of effectiveness may be developed. Total number of subjects in a Phase I drug trial generally is small (e.g. 20 to 80). Generally VA does not conduct many Phase 1 trials.

Definition: Phase 2- This is a second phase of a drug development and typically involves controlled clinical studies to evaluate effectiveness for a particular indication and to determine the common short-term side effects. It usually involves no more than a few hundred subjects.

When to use the VA Phase 1/2 Clinical CRADA model:

This model should be used in those clinical trials where the collaborator is the Sponsor, holds the IND, and has substantially developed the protocol. Under this CRADA model, VA is receiving a proprietary experimental compound (Test Article) from the collaborator. In phase 1/ 2 trials, there is still the possibility of an invention.

4. Phase 3/ 4 Clinical CRADA:

Definition: Phase 3- This trial expands controlled studies to gather additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship and to provide an adequate basis for product labeling. These studies are commonly prospective,

randomized, double-blind trials that compare an investigational drug product to a placebo or an existing therapy. Phase 3 studies generally involve several hundred to several thousand subjects.

Definition: Phase 4- In this trial, drug products may continue to be tested or analyzed after they have been approved for commercial marketing. Post approval studies are commonly referred to as Phase 4 studies. These studies may be intended to confirm predicted product characteristics, to gather information about the benefits and risks of a product in a larger, more diverse population and an uncontrolled setting, to obtain longer-term information about a product, or to evaluate a drug product for new intended uses. These studies have quite varied designs and study sizes.

When to use the Phase 3/ 4 Clinical CRADA model:

The phase 3/ 4 clinical CRADA models are used when the collaborator has substantially developed the protocol and the VA is receiving proprietary compound (Test Article) from the collaborator. In these studies, the collaborator is the Sponsor and holds the IND. Most safety and efficacy work has been completed. In a phase 3/4 trial, there is less chance of an invention; therefor, the collaborator is granted more rights to any intellectual property that may be developed under the agreement.

In cases where there is a further analysis of data from subjects who previously received a drug, but are not currently being treated with the drug, we normally use the phase 4 clinical CRADA model, rather than the Data Collection Agreement. These are sometimes referred to as post market studies. We select this model for the Phase 4 or post market studies because if there is the possibility that the collaborator will receive individually identifiable data or samples derived from humans we want to insure that proper human subject protection language is in the agreement. It is easier to remove language that is unnecessary, than to attempt to add human subject protection language into an agreement.

5. Investigational Device Clinical CRADA

Investigational device studies are clinical studies involving an investigational device (i.e. a stent, a prosthetic) that is subject to FDA oversight. There are a variety of medical devices being used in clinical settings; however, not all are subject to FDA oversight. Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices. In addition, medical devices include in vitro diagnostic products, such as general purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology. Certain electronic radiation emitting products with medical application and claims meet the definition of medical device. Examples include diagnostic ultrasound products, x-ray machines and medical lasers. The rules for devices which are subject to FDA oversight frequently change. For example, the FDA recently updated its guidance on mobile medical applications (apps). **The collaborator will be able to tell you if the device is subject to FDA oversight.**

A device for which FDA has oversight responsibilities will be classified by FDA. (See FDA website). Classification identifies the level of regulatory control that is necessary to assure the safety and effectiveness of a medical device. Most importantly, the classification of the device will identify, unless exempt, the marketing process (either premarket notification [510(k)] or premarket approval (PMA)) the manufacturer must complete in order to obtain FDA clearance/approval for marketing. The FDA defines *Investigational device* to mean a device that is the object of an investigation. The FDA further defines *investigation* to mean a clinical investigation or research involving one or more subjects to determine the safety or effectiveness

of a device. Again, the collaborator will be able to tell you if the device is subject to FDA oversight.

Under an Investigational Device Clinical CRADA, the protocol may be developed by the VA investigator or the collaborator.

When to use the Investigational Device Clinical CRADA model:

This CRADA model is used for clinical research involving the use of a device that is subject to FDA oversight. If the study involves the use of a device not subject to FDA oversight or uses equipment and human subjects are not involved in the study, then the Basic CRADA should be selected. We use the Investigational Device CRADA even in cases where the PI has developed the protocol due to the special terms related to devices that are in the agreement.

Note: The collaborator must supply the device free of charge. If the collaborator does not provide the device free of charge, you must contact the Technology Transfer Program (TTP) as the formal policy regarding the purchase of devices for use in research is under development.

6. Data Collection Agreement

The Data Collection Agreement is used for studies which involve a retrospective or prospective collection of data from patient medical records. The collaborator is <u>not</u> receiving individually identifiable information. The collaborator is not providing a Test Article or Investigational device under this kind of agreement.

When to use the DATA Collection model:

In order to use this template, <u>all</u> of the following conditions must be followed.

- The Statement of work (SOW) calls for the retrospective or prospective collection of data from patient medical records, such as registries, data mining and outcomes analysis;
- The SOW does not call for any interaction with subjects; the collaborator does not receive any materials derived from humans;
- The Collaborator is not seeking individually identifiable information;
- No intellectual property is anticipated from the project and neither party is interested in pre-commitment of intellectual property rights; and
- The Collaborator funds the project.

7. **Material Transfer CRADA**

The Material Transfer CRADA allows VA to receive proprietary materials, from a collaborator. The collaborator does not make an intellectual contribution to the study and only receives a summary of any results. The agreement allows VA to provide the collaborator with an option to take a license to any invention that may arise during the course of the research.

When to use the Material Transfer CRADA model:

The Material Transfer CRADA is use when VA 1) is receiving only research material (no funding); 2) the material is to be used only for non-human research; and 3) the provider of the material requires commitment of intellectual property rights in advance of supplying the material.

8. Material Transfer Agreement (MTA)

The Material Transfer Agreement (MTA) is **only** for use with non-profit or academic recipients. Unlike a CRADA, neither a licensing option nor rights for commercial purposes may be granted.. Generally these agreements are unilateral in nature, the VA is providing or receiving materials, and no collaboration is anticipated. An MTA is **not used** where the provider or recipient is a for-profit organization or company. In addition, this document is **not used** when the research material will be utilized for screening, production or sale. In the event that a for-profit organization or company will be providing materials to the VA, a Material Transfer CRADA must be used. If the for-profit organization or company will be receiving materials from the VA, then a license is used. In such a case, contact TTP.

Please note that many non-profit agencies will request that VA accept the UBMTA (Uniform Biological Materials Transfer Agreement) or the UBMTA implementing letter (found here). The NIH has also created three material transfer agreements. The NIH model MTAs are found here. These models may be accepted from non-profit agencies if they have not been modified.

When to use the Material Transfer Agreement:

The MTA may only be used when VA is the recipient or provider of material and no intellectual property (patent) rights are transferred. If VA is the recipient of a material and the provider would like a commitment of intellectual or patent rights, please use the Material Transfer CRADA. Unmodified MTAs may be approved locally and signed by the ACOS for Research so long as an appropriate delegation of authority has been put in place. Please contact OGC to coordinate a delegation letter.