UNITED STATES PUBLIC HEALTH SERVICE
TECHNOLOGY TRANSFER PROCEDURE MANUAL

Chapter No. 400.1

NIH Cooperative Research and Development Agreement Procedures

A. PURPOSE

The purpose of this National Institutes of Health (NIH) Technology Transfer Procedure Manual Chapter is to set forth the procedures for use of Cooperative Research and Development Agreements (CRADAs) within NIH laboratories or programs.[1]

B. BACKGROUND

The primary mission of the Public Health Service (PHS) is to pursue new knowledge through the conduct and support of research to improve the public health. In pursuit of this mission, NIH, as a PHS Agency, supports a broad spectrum of research approaches, ranging from basic laboratory research to clinical research. This continuum of research activities creates a synergism essential to the effective advancement of knowledge. The synergy that exists among these research approaches is dependent upon the ability of NIH researchers to discuss and explore new ideas freely and openly.

The Federal Technology Transfer Act (FTTA) of 1986, and Executive Order No. 12591, mandated PHS to encourage and facilitate collaborations, including via CRADAs, among NIH/PHS, state and local governments, universities, the private sector, particularly small businesses, and other entities in order to assist in the transfer of federal technology to the marketplace. The intent of Congress in authorizing CRADAs was to promote national technological competitiveness and the rapid transfer of the fruits of innovation to the marketplace.[2]

[1] "NIH laboratory(-ies) or program(s)," as used in this chapter, refer to an intramural laboratory or laboratories within the NIH Institutes and Centers (collectively, ICs), and to an NIH IC extramural program or programs, respectively.
[2] See 15 U.S.C. § 3702.

C. DEFINITIONS

1. **CRADA**: an agreement authorized by the FTTA that governs a cooperative research and development project between one or more PHS laboratories[3] or Government-owned, contractor-operated laboratories and one or more Federal or non-Federal parties. CRADAs are distinguished from other types of collaboration agreements by the grant of license options to subject inventions developed under the CRADA to the Collaborator and the ability of NIH to receive funds from the Collaborator(s).

2. **Materials-CRADA (M-CRADA)**: a type of CRADA under which the NIH obtains essential proprietary research material(s) and associated information from an outside party for a specific research project which is performed primarily by the NIH investigator. Provision of the proprietary research materials and associated information by the outside party is considered that party's collaborative contribution. Research materials that are obtained via an M-CRADA are generally not reasonably available from another commercial or academic source.

3. **Letter of Intent (LOI)**: a letter executed by authorized officials of an NIH Institute or Center (IC) and a collaborator reciting the parties' intent to enter into a CRADA and to begin the research prior to execution of the CRADA. CRADA research can be initiated under an LOI. An LOI packet includes the Letter, a Research Plan for the work that will be conducted under the LOI term, and the CRADA which will govern during the term of the LOI. Certain provisions of the CRADA will have an effective date of the LOI that describes those provisions.

4. **Collaborator**: the entity(ies) with whom the NIH is pursuing collaborative research under a CRADA.

5. **Collaborator Principal Investigator (Collaborator PI)**: the researcher responsible for the conduct of the research plan on behalf of the CRADA Collaborator.

6. **NIH Deputy Ethics Counselor (DEC)**: the individual within an IC assigned the responsibility for assessing conflict of interest for NIH personnel involved in CRADAs, as appropriate.

7. **NIH Principal Investigator (PI)**: a tenured or tenure-track scientist, a Senior Scientist, or Senior Clinician in the intramural research program who initiates, directs, and is responsible for the conduct of the CRADA on behalf of the NIH. Additionally, NIH

[3] "PHS laboratory (-ies)," as used in this chapter, refers to "Federal laboratory (–ies)" as described in the Federal Technology Transfer Act (FTTA) of 1986, 15 U.S.C. § 3701 et seq. As such, within the PHS, the National Institutes of Health (NIH), the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) are each a "Federal laboratory."

Staff Clinicians in the designation Associate Research Physician or Senior Research Physician with prior approval from their leadership may also function as a CRADA NIH Principal Investigator.

8. **NIH Extramural Investigator/Officer (EM I/O)**: Extramural staff (to be determined by an NIH Extramural Senior Official) who is responsible for the conduct and/or management of the CRADA on the behalf of the NIH.

9. **NIH Extramural Senior Official (EM SO)** (e.g., Division Director or Director of Extramural Activities): An Extramural Senior Official who has the authority to:

    a. approve participation of the NIH IC in the CRADA;
    b. assess and concur with the scientific merit and scope of the CRADA; and
    c. affirm that it is appropriate to allocate IC resources to the CRADA.

10. **NIH CRADA Subcommittee (NIH CS) of the PHS Technology Transfer Policy Board (TTPB)**: an internal committee that provides advice to the Director, NIH, on the NIH CRADA program. The NIH CS ensures that the NIH CRADA program is consonant with existing scientific, administrative, and legal policy of the NIH.

11. **NIH Office of Technology Transfer (NIH OTT)**: the NIH office with responsibility for providing administrative oversight of the NIH CRADA program and for maintaining a central NIH CRADA database.

12. **Technology Development Coordinator (TDC)**: the individual within an IC assigned responsibility for technology transfer, including the development, negotiation, execution and administration of CRADAs.

D. GENERAL NIH CRADA CONSIDERATIONS

Consistent with 15 U.S.C. § 3710a, the following considerations apply to NIH CRADAs:

1. Research under the CRADA

Although there is no restriction on the topic of research appropriate for a CRADA, all CRADA research projects must be highly focused and delineated, and each proposed CRADA must be carefully assessed for its overall research objectives. For example, a proposed CRADA would not be appropriate if the fundamental mission of the NIH and/or PHS is compromised by creating, either explicitly or indirectly, more than minimal constraints on research freedom and communication.

In considering a proposed CRADA, NIH Institutes or Centers (collectively, NIH ICs) will determine if the objectives of a proposed collaboration warrant the use of the CRADA mechanism or if its goals are more appropriately met through a

procurement contract, material transfer agreement, cooperative agreement, research collaboration, or other contractual mechanism. Sponsored research, such as routine, conventional testing, with no collaborative, intellectual contribution, is not appropriate for a CRADA. Also, the proposed collaborator's scientific and business capabilities will be assessed.

2. Ensuring Research Freedom

NIH investigators are generally free to choose the subject matter of their research, consistent with the mission(s) of PHS, NIH, their NIH IC, and the research in their laboratories or programs. This policy applies to CRADAs as well, and laboratories or programs and investigators have complete discretion to enter into or decline a CRADA collaboration.

CRADAs that explicitly attempt to direct NIH research are not appropriate. Additionally, in considering any proposed CRADA, attention must be given to whether directed research implicitly will be the net effect. For example, the greater the extent to which a laboratory's or program's resources derive from a CRADA, the less likely it will be that the laboratory or program will pursue other research opportunities outside of the CRADA; the broader the span of a CRADA research plan, the less able a laboratory or program will be to provide fair access and interact with others. The achievement of this balance will be considered in the decision-making process. Thus, consideration should be given to:

a. the fraction of a laboratory's or program's appropriated resources devoted to CRADA research;

b. the fraction of a laboratory's or program's total resources that derive from CRADA support, and the time and scope of work devoted to a given CRADA;

c. the amount of time that any one investigator would give to one or more CRADAs;

d. the number of CRADAs an investigator has with one entity;

e. the number of CRADAs a laboratory or program has with one entity; and

f. the number of CRADAs that any given entity might have with NIH and/or the NIH IC.

3. CRADA Funding

CRADA funds must be managed and accounted for by the IC investigator consistent with the terms of the CRADA and consistent with any applicable legal and regulatory requirements for administrative control of funds. For example, the terms of the CRADA may permit use of CRADA funds following termination of the CRADA, particularly if prematurely or unilaterally terminated by the CRADA Collaborator, such as for certain expenses related to completion of the Research Plan or continued funding of IC personnel for a specified period of time. Any CRADA funds remaining which cannot be spent consistent with the CRADA terms must be refunded to the CRADA Collaborator and cannot unilaterally be converted to gift funds by NIH ICs.

4. Scientific Communication and Dissemination of Research Results

Reasonable confidentiality requirements and brief delays in dissemination of research results are permitted under a CRADA, as necessary, in order to protect proprietary materials and intellectual property rights. CRADAs should not unreasonably restrict or constrain scientific interaction or the dissemination of research information. In considering any proposed CRADA, consideration must be given to the possibility that the level of confidentiality associated with that CRADA project might, on balance, inappropriately impair the degree of openness necessary to maintain effective scientific communication and to serve the public interest.

5. Avoidance of Conflict of Interest

In NIH EM programs, EM I/Os and EM SOs who administer grants and contracts may have an inherent conflict of interest that would preclude their participation in CRADAs. In NIH intramural laboratories, PIs also may have conflicts of interest, in that they serve as a project officer on a contract or have authority over funding decisions in the course of their research. In both cases, the employee may have financial interests that would be affected by their proposed CRADA. Therefore, any conflict of interest--actual or apparent--must be addressed and resolved by the PI, EM I/O, and EM SO with his/her IC DEC in the review and approval of CRADAs.

E. NIH CRADA PREPARATION, SUBMISSION AND REVIEW PROCEDURES

The following procedures are used at the NIH for the development, review, and administration of CRADAs.

1. Initiating a CRADA

Initiating a project to be conducted under a CRADA is based on scientific considerations and the desire for the public to benefit from the further development and commercialization of particular NIH research.

In conjunction with staff assigned by the IC TDC, the NIH investigator and the proposed collaborator develop a CRADA using a PHS model CRADA or a CRADA comprised of PHS approved CRADA language.

2. Components of a CRADA Package Submitted for NIH CS Review

The CRADA package consists of: (a) a cover memo to the NIH CS explaining the background to the project, confirming approved Conflict of Interest (COI) certification(s), any modifications of note and/or special issues and when clinical research is involved verification that, as appropriate, the IRB will be notified that there is an associated CRADA; (b) the CRADA clearance document; (c) an appropriate CRADA document, including the Summary Page which the parties agree can be publicly released; (d) the CRADA Research Plan; (e) information on Staffing, Funding and Material/Equipment Contributions of the Parties; (f) Modifications to PHS approved CRADA language, included within the model agreement (in redline/strikeout format) or set forth in a separate Appendix; and (g) any additional Appendix(ces) as needed. For M-CRADAs, the Research Plan is typically contained in Appendix A and the Modifications to the M-CRADA model are typically included within the model agreement (in redline/strikeout format) or set forth in a separate Appendix B.

a. CRADA Clearance Document

The CRADA Clearance Document records the approval of the CRADA by the IC; documents, when applicable, clinical research-related self-certifications by the PI, EM I/O, and EM SO; and provides an overview of CRADA information. Intramural (IM) and Extramural (IM) CRADAs each have a Clearance Document. The information collected in the IM/EM Clearance Documents includes descriptive and contact information for the IC and Collaborator participants, IC approval signatures, background intellectual property issues, and summary information related to clinical research, if applicable.

b. Approved COI Certification

The COI certification provides the self-certification by the PI, or EM I/O and

EM SO, that he/she will abide by the conflict of interest statutes, the government-wide standards of ethical conduct, the supplemental standards of ethical conduct applicable to NIH employees, and that he/she is responsible for identifying conflicts of interest, including apparent conflicts of interest, at the initiation and during the entire duration of the CRADA. The COI(s) certification and form are approved by the IC DEC.

c. CRADA Research Plan

The Research Plan defines the scope of the research conducted under the CRADA and reflects the goals and objectives of the participants, including the specific responsibilities of each party in carrying out the Research Plan. The scope of the Research Plan delineates the possible field of use of any license subsequently negotiated between the NIH IC and the Collaborator for any CRADA Subject Invention for which the Collaborator exercises its exclusive license option. A recommended CRADA Research Plan format includes:

(1) A brief introductory statement about the project which includes the scope of the project and the specific goal(s) of the NIH IC and Collaborator;

(2) An introduction to the project which includes a brief description of the scientific background to the collaborative undertaking so that the project and its scientific importance can be understood in context;

(3) A section setting out the experimental plan which the parties will undertake;

(4) The roles, responsibilities, and contributions of the NIH IC solely, the Collaborator solely, and the parties jointly. Such information can be listed in bullet format; and

(5) Each party's related background inventions and related technology transfer agreements.

d. Financial and Staffing Contributions of the Parties

Information related to staffing, funding, travel plans, and materials/equipment contributions of the Parties, as appropriate, is described in each Agreement.

e. Modifications to the Model CRADA

There are circumstances when it may be necessary to propose a modification to PHS-approved CRADA language. Any proposed revision to such language

is included, either within the agreement (in redline/strikeout format) or in a separate appendix to the Agreement. Changes are negotiated generally between the IC and the Collaborator. All changes recommended must be within NIH and PHS policy and meet Federal legal requirements. Similarly, there may be IC programs which would benefit from having a program-specific template generated by modifying the model CRADA to address an IC program's specific procedures and needs. Any such IC-specific program template CRADA can be proposed to the NIH CS for consideration.

f. LOI

The LOI is used primarily to permit collaborative research to begin between the NIH IC laboratory or program and a proposed CRADA collaborator prior to final approval by the NIH and execution of the CRADA; however, funds may not be transferred under the LOI. Any intellectual property rights that arise during this collaboration under the LOI may be considered, if appropriate, CRADA Subject Inventions, should the CRADA be executed.

3. Duration of CRADAs

The initial duration of CRADAs is typically 3-5 years with the possibility of extension as appropriate. M-CRADAs generally involve more limited research and typically have an initial duration of 1-3 years.

4. NIH Central Database

The NIH OTT maintains a computerized database of all NIH CRADAs. TDCs are expected to ensure inclusion of electronic copies of executed CRADAs and Amendments in this central database within ten (10) days of receipt by the IC of a fully executed CRADA or Amendment.

5. NIH CS CRADA Review Process

Review and approval of CRADAs by both the IC and NIH Office of the Director (OD) is required. IC review focuses on the scientific merit and relevance of the proposed activity as it relates to the IC's mission and assures that proposed resources are appropriate to the research proposal and the NIH laboratory or program operation.

On behalf of the NIH OD, the NIH CS provides a recommendation on behalf of the NIH Director as to whether to approve, disapprove or require modification to a CRADA. The NIH CS review ensures that the CRADA complies with NIH and PHS policy, that it is consistent with CRADAs from other NIH ICs, and that no patent and licensing, legal, policy, or administrative problems exist. NIH CS shall defer action on a CRADA until any legal or policy issue is clarified by the IC, OGC or TTPB, as may be appropriate.

F. POST-EXECUTION AMENDMENTS

Any amendment that significantly modifies the original CRADA, in particular those changes that expand the research plan, must be reviewed at the NIH level. The IC will determine when a CRADA amendment requires review and approval at the NIH level. The IC is authorized to approve any amendment which does not require NIH CS review including amendments that extend the term of a CRADA. Executed copies of all executed amendments must be included in the NIH central data system within ten (10) days of receipt by the IC of the fully executed CRADA amendment.

G. RESPONSIBILITIES

Below is a general outline of the duties and responsibilities of the various organizations and individuals involved in the review, approval, and administration of CRADAs.

1. IC:

a. PI (and EM I/O and EM SO, as appropriate)

- develop Research Plan, detailing contribution of each party and equipment needs
- determine IC staffing needs
- develop a budget for IC's research activities
- prepare any required annual summary and reports
- manage CRADA funds and participation in preparation of any required fiscal reports
- participate in determining that the Collaborator is scientifically capable of performing required research
- perform research described in the Research Plan
- inform TDC of any change in status of CRADA
- assure compliance with all NIH rules and regulations, including those applying to research with human subjects, animals, radioactive materials, biosafety, and recombinant DNA

- prepare conflict of interest form, including certification, for review by IC DEC and address and resolve any conflicts of interest, whether actual or apparent

- inform other researchers whose work may be considered part of the CRADA that the CRADA will govern Subject Inventions, creates a confidentiality obligation to the Collaborator, and should be considered in any ethics review

- when clinical research is conducted under a CRADA, the PI will inform the Chair of the appropriate IRB about the CRADA and provide the CRADA to the Chair, as appropriate. This will be done to assure that the CRADA and its obligations do not conflict with the requirements of the IRB, or interfere with any matters that currently fall within its jurisdiction or could reasonably be anticipated to do so in the future. Clinical research, as used in this chapter, refers broadly to research using any data or material that originated from a human or research in which a material is being used on, or in, a human

b. TDC

- assist IC personnel in determining if proposed research is appropriate for the CRADA mechanism

- draft the Research Plan

- ensure that the CRADA has significant intellectual contribution by all parties. For an M-CRADA, determine whether resources sought by NIH investigator are appropriate to seek via this type of CRADA

- negotiate CRADA terms

- review all CRADAs to assure compliance with PHS, NIH and IC policy and procedures

- assess resources, modifications to PHS-approved CRADA language, fair access issues, patent issues, and impact of CRADA on existing IC collaborations

- ensure that all CRADAs have been submitted for appropriate clearances to determine compliance with rules and regulations applying to conflict of interest, and research with human subjects, animals, radioactive materials, biosafety, and/or recombinant DNA

- ensure that the Collaborator is not identified in the Excluded Parties List System (https://www.epls.gov) as an organization debarred or suspended, or considered to be a high risk; does not owe a debt to the government, and has no outstanding reports or royalty payments with NIH OTT

- coordinate the review process, which includes submission of the CRADA to each appropriate IC and NIH reviewing organization

- as needed, provide outreach assistance to assure fair access to IC technologies

- serve as IC liaison with NIH OTT, OGC and NIH CS

- arrange for IC execution of CRADAs and amendments

- maintain all original CRADA files in a secure environment

- ensure inclusion of copies of executed CRADAs and amendments in NIH-managed central database

- ensure that the investigator recognizes responsibility to manage CRADA funds

- ensure ethics review

c. Scientific Director/Division Director

- assess and concur on scientific merit and scope of research plan

- concur on the relationship to the mission of the program and possible long-term impact on the laboratory/program and IC

- approve the investigator's effort and time (total commitment to CRADAs) in relation to entire work effort and level of the laboratory/program resources to be devoted to the individual CRADA and to CRADAs overall

- approve level of support to be provided; if CRADA resources are a significant fraction of a laboratory/program budget, an in-depth review may be required

d. IC Director

- sign and approve final CRADA or Amendment

- ensure ethics review including conflicts of interest

2. NIH OTT

   - coordinate NIH CS discussions and maintain associated records, including minutes, and disseminate results timely
   - develop and provide general oversight of CRADA policy and procedures
   - provide NIH CS recommendations to the ICs and advise the NIH CS on specific proposed CRADAs
   - provide advice and assistance to ICs in negotiating CRADAs, as necessary or upon request
   - maintain a centralized data base for CRADA records
   - respond to inquiries on NIH and PHS CRADA activities

3. OGC

   - provide legal advice and assistance to ICs in negotiating CRADAs and amendments, as necessary or upon request
   - provide clearance for legal sufficiency of proposed CRADAs during consideration by the NIH CS

4. NIH CS

   - review CRADAs and ensure they are consistent with existing policy
   - recommend CRADA policies and procedures to the TTPB
   - advise Director, NIH, whether to disapprove an individual CRADA

5. Director, NIH

- promulgate NIH CRADA policy
- approve and disapprove CRADAs and amendments, as necessary

6. IC DEC

- Review ethics records of the PI(s), EM I/O(s) and EM SO, to determine whether it appears that the investigator(s) will violate any government ethics rule, as of date of review, should the proposed CRADA be approved

H. EFFECTIVE DATE

The procedures set forth in this Manual Chapter are effective February 1, 2021, and supersede in their entirety PHS Technology Transfer Manual Chapter 402, which was first approved on May 23, 1996 and revised in part on March 17, 2009 and on March 8, 2012.

I. ADDITIONAL INFORMATION

For more information on this Manual Chapter, contact the Office of Technology Transfer, NIH, (301) 496-7057 or http://www.ott.nih.gov/contactus/contact_us.aspx.