**PUBLIC HEALTH SERVICE**

**COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT**

**FOR NCI DIVISION OF CANCER TREATMENT AND DIAGNOSIS (DCTD) EXTRAMURAL PHS CLINICAL AND NON-CLINICAL RESEARCH**

This Agreement is based on the model Cooperative Research and Development Agreement (“CRADA”) adopted on December 8, 2010 by the U.S. Public Health Service (“PHS”) Technology Transfer Policy Board for use by components of the National Institutes of Health (“NIH”), the Centers for Disease Control and Prevention (“CDC”), and the Food and Drug Administration (“FDA”), which are agencies of the PHS within the Department of Health and Human Services (“HHS”).

This Cover Page identifies the Parties to this CRADA:

The U.S. Department of Health and Human Services, as represented by

**National Cancer Institute**

an Institute or Center (hereinafter referred to as the “NCI”) of the

**National Institutes of Health**

 and

**[Pharmaceutical Collaborator’s Name].**,

hereinafter referred to as the “Collaborator,”

having offices at [HQ address],

created and operating under the laws of [US Stae]

Collectively or individually, each shall also be referred to as a Party or Parties.

**COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT**

**FOR EXTRAMURAL-PHS CLINICAL AND NON-CLINICAL RESEARCH**

**Article 1. Introduction**

This CRADA between NCI and Collaborator will be effective when signed by the Parties, which are identified on both the Cover Page and the Signature Page. The official contacts for the Parties are identified on the Contacts Information Page. Publicly available information regarding this CRADA appears on the Summary Page. The research and development activities that will be undertaken by NCI Approved Investigators and Collaborator in the course of this CRADA are detailed in the Research Plan, attached as Appendix A. An example of typical terms for an MTA for the transfer of Investigational Agent from NCI to Approved Investigator for conducting any approved Protocol or Proposal is attached as Appendix B. Since CTEP and DCTD (defined below) within the NCI are responsible for the Research Plan, NCI, DCTD and CTEP may be used interchangeably in this Agreement when a specific program is responsible for an activity.

**Article 2. Definitions**

The terms listed in this Article will carry the meanings indicated throughout the CRADA. To the extent a definition of a term as provided in this Article is inconsistent with a corresponding definition in the applicable sections of either the United States Code (U.S.C.) or the Code of Federal Regulations (C.F.R.), the definition in the U.S.C. or C.F.R. will control.

“**Adverse Event**” or “**AE**” means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, as defined under 21 C.F.R § 312.32. See also FDA Good Clinical Practice Guideline (International Conference on Harmonisation (ICH) E6: “Good Clinical Practice: Consolidated Guidance, 62 Federal Register 25, 691 (1997)).

“**Affiliate**” means any corporation or other business entity controlled by, controlling, or under common control with Collaborator at any time during the term of the CRADA. For this purpose, “control” means direct or indirect beneficial ownership of at least fifty percent (50%) of the voting stock or at least fifty percent (50%) interest in the income of the corporation or other business entity.

“**Annual Report**” or “**IND Annual Report**” means the report of progress of an IND-associated investigation that the Sponsor must submit to the FDA within sixty (60) days of the anniversary of the effective date of the IND (pursuant to 21 C.F.R. § 312.33).

**“Approved Investigator”** means an investigator responsible for serving as the lead researcher of a clinical or non-clinical study and who (i) is not an NCI employee; (ii) is approved to participate in the NCI Formulary; (iii) has (or will have) executed a NCI Formulary Material Transfer Agreement in the form attached as Appendix B (“MTA”); (iv) in the case of a clinical Study, is a Clinical Investigator as well as the Sponsor for such Study/Protocol; and (v) has submitted a Protocol/Proposal which is approved by Collaborator in accordance with Section 3.2.

 “**Clinical Investigator**” means, in accordance with 21 C.F.R. § 312.3, an individual who actually conducts a clinical investigation, that is, who directs the administration or dispensation of Formulary Agent to a subject, and who assumes responsibility for studying Human Subjects, for recording and ensuring the integrity of research data, and for protecting the welfare and safety of Human Subjects. For the purpose of this CRADA, the Clinical Investigator will be the Approved Investigator, who is (i) not an NCI employee and has current investigator registration documents on file with the PMB, NCI; and (ii) from a Clinical Research Site that has been audited at least once within the past 3 years by the NCI/CTEPin accordance with the NCI/CTEP/CTMB Audit Guidelines (see:<http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmb_audit_guidelines.pdf>)

“**Clinical Research Site(s)**” means the site(s) at which the Protocol(s) described in the Research Plan will be performed.

“**Confidential Information**” means confidential scientific, business, financial information, or Identifiable Private Information provided that Confidential Information does not include:

(a) information that is publicly known or that is available from public sources;

(b) information that has been made available by its owner to others without a confidentiality obligation;

(c) information that is already known by the receiving Party, or information that is independently created or compiled by the receiving Party without reference to or use of the provided information; or

(d) information that relates to potential hazards or cautionary warnings associated with the production, handling, or use of the Formulary Agent.

“**Cooperative Research and Development Agreement**” or “**CRADA**” means an agreement, entered into pursuant to the Federal Technology Transfer Act of 1986, as amended (15 U.S.C. §§ 3710a *et seq*.), and Executive Order 12591 of April 10, 1987.

“**CRADA Collaborator Principal Investigator(s)**” or “**CRADA Collaborator PI(s)**” means the person(s) who will be responsible for the scientific and technical conduct of the Research Plan on behalf of the CRADA Collaborator.

“**CRADA Data**” means information developed by or on behalf of the Parties (including information developed by Approved Investigators as well as all personnel assisting the Approved Investigators in the performance of research under this CRADA and an applicable MTA) in the performance of the Study(ies) of Research Plan, excluding Raw Data.

**“CTEP”** means the Cancer Therapy Evaluation Program, DCTD, NCI, a program within NCI that plans, assesses and coordinates all aspects of clinical trials including extramural clinical research programs, internal resources, treatment methods and effectiveness, and compilation and exchange of data.

**“DCTD”** means Division of Cancer Treatment and Diagnosis, NCI, NIH

“**Effective Date**” means the date of the last signature of the Parties executing this Agreement.

“**Government**” means the Government of the United States of America.

“**Human Subject**” means, in accordance with the definition in 45 C.F.R. § 46.102(f), a living individual about whom an investigator conducting research obtains:

(a) data through intervention or interaction with the individual; or

(b) Identifiable Private Information.

“**Identifiable Private Information**” or “**IPI**” about a Human Subject means private information from which the identity of the subject is or may readily be ascertained. Regulations defining and governing this information include 45 C.F.R. Part 46 and 21 C.F.R. Part 50.

“**IND**” means an “**Investigational New Drug Application**,” filed in accordance with 21 C.F.R. Part 312 under which clinical investigation of an experimental drug or biologic (Investigational Agent) is performed in Human Subjects in the United States or intended to support a United States licensing action.

“**Institutional Animal Care and Use Committee”** or “**IACUC**” means, in accordance with the Animal Welfare Act codified in Title 9 C.F.R., Chapter 1, Subchapter A - Animal Welfare, Parts 1, 2, and 3, an institutional committee established to protect the welfare of animals used in research and education.

“**Institutional Review Board**” or “**IRB**” means, in accordance with 45 C.F.R. Part 46, 21 C.F.R. part 56, and other applicable regulations, an independent body comprising medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of the Human Subjects involved in a study.

 “**Invention**” means any invention or discovery that is or may be patentable or otherwise protected under Title 35 of the United States Code, or any novel variety of plant which is or may be protectable under the Plant Variety Protection Act, 7 U.S.C. §§ 2321 et seq.

 “**Investigational Agent**” or “Investigational New Drug” means, in accordance with the definition in 21 C.F.R. § 312.3, a new drug or biological drug that is used in a clinical investigation. For this Agreement, Investigational Agent means Collaborator’s proprietary investigational agents as listed in Attachment A, provided by or on behalf of Collaborator. For the purpose of this CRADA, Investigational Agent(s) will be referred to as “**Formulary Agent(s)**”.

“**Investigator’s Brochure**” means, in accordance with the definition in 21 C.F.R. § 312.23(a)(5), a document containing information about the Investigational Agent, including animal screening, preclinical toxicology, and detailed pharmaceutical data, including a description of possible risks and side effects to be anticipated on the basis of prior experience with the drug or related drugs, and precautions, such as additional monitoring, to be taken as part of the investigational use of the drug.

**“Multi-Party Data”** means data from studies pursuant to CRADAs, where such data are collected under approved Protocols or Proposals involving combinations of Formulary Agents supplied from more than one NCI CRADA collaborator.

**“NCI Formulary Material Transfer Agreement”** or **“MTA”** means an MTA executed between NCI and an Approved Investigator and his/her Research Site for the conduct of the Study.

“**NIH CRADA Extramural Investigator/Officer(s)**” means the extramural staff who are responsible for the conduct and/or management of the CRADA on behalf of the NIH. In the case of this CRADA, the NIH CRADA Extramural Investigator is Dr. Jeffrey Moscow and the NIH CRADA Extramural Officer is Dr. Margaret Mooney.

**Non-Clinical Investigator** is an investigator who (i) is the principal investigator for a Proposal; (ii) is approved by NCI and Collaborator to participate in the NCI Formulary; (iii) has (or will have) executed a MTA;; (iv) has submitted a Proposal which is approved by Collaborator; and (v) conducts the approved Proposal at an institution in the United States or internationally.

“**Non-Clinical Research Site(s)**” means the site(s) at which the approved Proposal(s) or Non-Clinical Study(ies) described in the Research Plan will be conducted.

“**Non-Clinical Study(ies)**” means any Proposal(s) that has been approved by Collaborator to be conducted by a Non-Clinical Investigator serving as an Approved Investigator under this CRADA.

“**Non-Clinical Study Proposal**” or “**Formulary Proposal**” means the non-clinical investigation in which a drug is used in vivo or in vitro. It proposes and describes the objective(s), design, methodology, statistical considerations, and organization of a research study, which requires Collaborator’s written approval to be covered by this CRADA. For the purposes of this CRADA, such Proposal, if for non-clinical research involving any animals, shall include any and all associated documents required by the applicable IACUC.

 **“PMB”** means Pharmaceutical Management Branch within the Division of Cancer Treatment and Diagnosis which is charged with providing pharmaceutical support for clinical trials sponsored by DCTD, NCI.

 “**Protocol**” or “**Formulary Protocol**” means the clinical investigation in which a drug is administered or dispensed to, or used involving, one or more human subjects. It describes the objective(s), design, methodology, statistical considerations, and organization of a trial. For the purposes of this CRADA, such Protocol, for clinical research involving Human Subjects, shall include any and all associated documents, including informed consent forms, to be provided to Human Subjects and potential participants in the study.

“**Raw Data**” means the primary quantitative and empirical data first collected from experiments in approved Proposals and/or Protocols conducted within the scope of this CRADA. The relevant MTA will provide the details regarding Raw Data to be provided by the Approved Investigator to the Collaborator.

“**Research Plan**” means the statements in Appendix A of the respective commitments of the Parties, which automatically includes any Formulary Protocols or Proposals approved under this CRADA in the Research Plan. The provisions for sponsoring the IND, clinical and safety monitoring, and data management are set forth therein.

“**Research Site**” means Clinical Research Sites and/or Non-Clinical Research Sites.

“**Sponsor**” means in accordance with the definition in 21 C.F.R. § 312.3, an organization or individual who assumes responsibility for supervising or overseeing clinical trials with Formulary Agents, and is sometimes referred to as the IND holder. For all Protocols under this CRADA, the IND Sponsor will be the Clinical Investigator or his/her Clinical Research Site.

“**Study**” means each Clinical or Non-Clinical Study described, respectively, by a Protocol or Proposal submitted and approved in accordance with Section 3.2.

**Article 3. Cooperative Research and Development**

3.1 **Performance of CRADA Activities**. The activities to be carried out under this CRADA will be performed by the Parties identified on the Cover Page as well as by Approved Investigators as described in the approved Protocol(s) or Proposal(s). Approved Investigators will be responsible for conducting such approved Clinical or Non-Clinical Studies included in the Research Plan.

3.2 **Research Plan**.

 3.2.1 **Clinical** **Protocol**

(a) NCI will facilitate the solicitation and receipt of LOIs for clinical research, contemplating the use of Collaborator’s Formulary Agents. NCI will require potential Sponsors to complete a “Letter of Intent” (“LOI”). NCI will provide Collaborator with a copy of any LOI submitted which requests use of Collaborator’s Formulary Agents, which contains a summary of the draft clinical protocol including the proposed statistical analysis plan for the Study and, estimated funding from the Collaborator to support the Study.

(b) Within 60 days of receipt of a Letter of Intent from NCI, Collaborator shall provide a written notice to IC whether or not it approves the LOI. Acceptance of an LOI shall be Collaborator’s sole discretion.

• If Collaborator notifies NCI of its rejection of the LOI within such 60-day period, then neither Party shall have any obligations to the other with respect to the proposed Study or any drug supply in respect of such Study.

• If Collaborator notifies NCI within such 60-day period that it approves the LOI with a signed drug approval form, the Approved Investigator will draft and submit a full clinical Protocol(s) for approval by Collaborator.

• Following the LOI approval, the Parties (or their respective designated Affiliate) will, as soon as reasonably practicable following such notification, arrange communications between PMB staff and Collaborator supply personnel to discuss logistics.

• Any changes to the Protocol shall require Collaborator’s prior written consent. Any such proposed changes will be sent in writing to Collaborator by Approved Investigator.

3.2.2 **Non-Clinical Proposal**.

1. NCI will facilitate the solicitation and receipt and approval of Proposals for Non-Clinical Studies contemplating the use of Collaborator’s Formulary Agents.
2. Within 10 (ten) business days of receipt of a Formulary Proposal forwarded by NCI, Collaborator shall provide a written notice to NCI whether or not it approves the Proposal at Collaborator’s sole discretion.
3. NCI will provide a draft MTA (see Appendix B) to the Non-Clinical Investigator and the relevant Institution for insertion of a research plan and signatures. Such Non-Clinical Investigator will then return the partially executed MTA to NCI.
4. Upon full execution of the MTA, NCI will return a copy to both Collaborator and the Non-Clinical Investigator.
5. Collaborator will ship the Formulary Agent directly to the Non-Clinical Investigator.

3.3 **Disclosures to NCI**. Prior to execution of this CRADA, Collaborator agrees to disclose to NCI all instances in which outstanding royalties are due under a PHS license agreement and in which Collaborator had a PHS license terminated in accordance with 37 C.F.R. § 404.10. These disclosures will be treated as Confidential Information upon request by Collaborator in accordance with the definition in Article 2 and Paragraphs 8.3 and 8.4.

3.4 **Approved Clinical and Non-Clinical Investigator Responsibilities**.

3.4.1 NCI will ensure that the Clinical Investigator will be required to submit, or to arrange for submission of, each Protocol associated with this CRADA to all appropriate IRBs, and for ensuring that the IRBs are notified of the role of Collaborator in the Study. In addition to the Protocol, all associated documents, including informational documents and advertisements, must be reviewed and approved by the appropriate IRB(s) before starting the clinical Study at each Clinical Research Site. The Study will be done in strict accordance with the Protocol(s) and no substantive changes in a finalized Protocol will be made unless mutually agreed upon, in writing, by the Parties. The Study shall not commence (or will continue unchanged, if already in progress) until each substantive change to a Protocol, including those required by either the FDA or the IRB, has been integrated in a way acceptable to the Parties, submitted to the FDA (if applicable) and approved by the appropriate IRBs.

3.4.2 For animal studies that are involved in an approved Non-Clinical Study, NCI will ensure that the Non-Clinical Investigator is required to submit, or to arrange for submission of, each Proposal for an animal Study that is associated with this CRADA to the appropriate IACUC and for obtaining any requisite approvals from such IACUC, and that the animal research will be done in strict accordance with the Proposal(s), as approved by the IACUC, and no substantive changes in a finalized Proposal will be made unless mutually agreed upon, in writing, by the Parties.

3.5 **Investigational New Drug Applications**.

3.5.1 Approved Clinical Investigator will be the IND Sponsor for the clinical Study and will be responsible for all regulatory submissions to the FDA concerning the Study. Approved Investigator will cross-file on Collaborator’s IND and/or DMF, to the extent applicable, and will be responsible for all applicable regulatory information. All Approved Investigators participating in clinical trials must have current investigator registration documents (Form 1572, Financial Disclosure, NIH Biosketch) on file with the NCI for the purposes of identifying Approved Investigators qualified to participate on the NCI Formulary Study and for the purpose of trial conduct using NCI’s clinical trial infrastructure, but are also required to maintain their own Form FDA 1572 and Form FDA 3455 as Sponsor -investigator in accordance with 21CFR312 and 21CFR54, respectively.

3.5.2 Collaborator may sponsor its own clinical trials and hold its own IND for studies performed outside the scope of each clinical Study conducted in accordance with this CRADA. All data from those clinical trials are proprietary to Collaborator for purposes of this CRADA.

3.6 **Formulary Agent Information and Supply**.

3.6.1 Collaborator agrees to provide DCTD without charge and on a schedule that will ensure adequate and timely performance of the Studies, and a sufficient quantity of formulated and acceptably labeled, clinical-grade Formulary Agent to complete the Protocol(s) agreed to and approved under this CRADA. Collaborator will provide a lot-release Certificate of Analysis to DCTD for each lot of the Formulary Agent provided for such clinical Study. Collaborator will also provide DCTD with a copy of the Formulary Agent Material Safety Data Sheet as requested by DCTD. It is understood that DCTD shall take responsibility for and reasonable steps to maintain appropriate records and assure appropriate supply, handling, storage, distribution and usage of these materials in accordance with the terms of this Agreement, the Protocol(s), and any applicable laws and regulations relating thereto.

 NCI will not ship Formulary Agent(s) until it receives the Approved Investigator(s)’s IRB Approval Letters, FDA “Study May Proceed” letter, and any revised Protocols responding to the same, as described in the MTA.

3.6.2 Collaborator agrees to supply sufficient inventory to ensure adequate and timely supply of Formulary Agent for mutually agreed upon Protocol(s), Proposal(s), and forecasts. DCTD will provide updated forecasts of amounts of Formulary Agent anticipated for ongoing and anticipated Protocols and the Parties agree to discuss in good faith any material changes or concerns regarding the updated forecast. Collaborator further agrees to provide draft Formulary Agent label to the NCI Pharmaceutical Management Branch (PMB) for review. Collaborator and PMB agrees to discuss any concerns over product labeling and agree to come to a mutually acceptable label for both Parties. If Possible, NCI prefers the NCI NSC (National Service Center) number for the Formulary Agent to be on the label. Alternatively, Collaborator can provide the commercial Formulary Agent supply label that complies with applicable regulations, and commercially labeled Formulary Agent is suitable for use in the Protocols hereunder.

3.6.3 Collaborator agrees to provide directly to the PMB the Investigator's Brochure (IB) for each Formulary Agent and all subsequent revisions/editions within three (3) weeks of such revisions/editions. The Investigator’s Brochure and all subsequent updates/revisions will be provided for the purpose of protocol development and protocol conduct. Electronic versions of copies provided to PMB should be emailed to the IB Coordinator at IBCoordinator@mail.nih.gov.

3.6.4 Notwithstanding the foregoing, Collaborator will provide directly to Non-Clinical Investigators suitable amount of Formulary Agent as needed for any approved Proposals in accordance with the corresponding executed MTA. PMB will not distribute Formulary Agent to Non-Clinical Investigators.

3.7 **Formulary Agent Delivery and Usage**. Collaborator will ship the Investigational Agent to NCI or its designee in containers marked in accordance with 21 C.F.R. § 312.6 for any Protocol(s) of the CRADA. NCI will ensure that the Approved Clinical Investigators are required to keep appropriate records and take reasonable steps to ensure that the Formulary Agent is used in accordance with the Protocol(s), Proposal(s), and applicable FDA regulations. In addition, NCI will ensure that the Formulary Agent (and all Confidential Information supplied by Collaborator relating to the Formulary Agent) will be used solely for the conduct of the CRADA Research Plan. Furthermore, NCI will ensure that no analysis or modification of the Formulary Agent will be performed by Approved Investigators without Collaborator’s prior written consent. At the completion of the Research Plan, any unused quantity of Formulary Agent in NCI’s possession will be returned to Collaborator, at Collaborator’s expense, or disposed as directed by Collaborator. The contact persons for PMB and Collaborator are identified on the Contacts Information Page.

3.8 **Auditing and** **Monitoring of Protocols**.

3.8.1 NCI will ensure that Clinical Investigators must be from Clinical Research Sites that have been audited at least once within the past 3 years by the NCI/CTEPin accordance with the NCI/CTEP/CTMB Audit Guidelines (see:  <http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmb_audit_guidelines.pdf>) and have had an Acceptable rating (i.e., Acceptable or Acceptable with F/U rating) for the most recent audit.  An investigator from a Clinical Research Site that has a history of Unacceptable audits or Unacceptable ratings will not be able to participate in Protocols under this Agreement.  NCI will ensure that Clinical Studies must be conducted by Approved Investigators in accordance with the FDA Good Clinical Practices (GCP) and, if required by the applicable Proposal, Non-Clinical Studies must be conducted in accordance with the FDA Good Laboratory Practices (GLP).

3.8.2 Collaborator or its designee(s) canmakearrangements with the Clinical Research Sites to audit the conduct of the clinical research and to obtain updates on ongoing clincial Studies at times convenient to Clinical Research Sites.  Collaborator may also make arrangements with Research Sites to audit and verify Raw Data and source documents, at the completion of a Protocol and at Collaborator’s expense, to the extent necessary to verify compliance with the federal regulations, Good Clinical Practice (GCPs) and the Protocol to ultimately ensure patient safety and/or Good Laboratory Practice (GLPs) and the Proposal.  Although NCI will continue to audit the Clinical Research Sites participating in the Formulary, NCI/CTEP will not be monitoring or auditing any Protocol under this CRADA.

**Article 4. Reports**

4.1 **Interim Research Plan Reports**.

 (a) NCI will ensure that each Clinical Investigator of the approved Protocol shall provide Collaborator with quarterly reports that outline the progress of the approved Protocols under this CRADA. More detailed information may be obtained by Collaborator directly from the Clinical Research Sites.

 (b) NCI will ensure that each Non-Clinical Investigator of the approved Proposal shall provide Collaborator with bi-annual study reports that outline the progress of the approved Proposals. More information or updated may be obtained by Collaborator directly from such Non-Clinical Investigator.

4.2 **Final Research Plan Reports**. NCI shall ensure that Approved Investigator will provide to Collaborator a final report of their clinical or non-clinical Study results within six (6) months after the completion or termination of each Study under this CRADA. These reports will set forth the technical progress made and any publications arising from the Study. Abstracts and publications provided to CTEP by Approved Investigators and further provided by CTEP to Collaborator shall fulfill this final report obligation. With respect to clinical Studies, a copy of the IND(s) Annual Report will also fulfill this reporting obligation.

4.3 **Fiscal Reports**. If Collaborator has agreed to provide funding to NCI under this CRADA and upon the request of Collaborator, then concurrent with the exchange of final Research Plan reports according to Paragraph 4.2, NCI will submit to Collaborator a statement of all costs incurred by NCI for the CRADA. If the CRADA has been terminated, NCI will specify any costs incurred before the date of termination for which NCI has not received funds from Collaborator, as well as for all reasonable termination costs including the cost of returning Collaborator property or removal of abandoned Collaborator property, for which Collaborator will be responsible.

4.4 **Safety Reports in Clinical Studies**.

 (a) NCI shall ensure the following:

1. The IND Sponsor (or Clinical Investigators of Protocol) shall report all serious and unexpected adverse events involving the Formulary Agent to FDA in accordance with the reporting obligations of 21 CFR 312.32 and will, concurrently, forward copies of all such reports, including the initial report no later than one (1) working day from receipt, and the final report slated for submission, to Collaborator and/or Collaborator’s designee, and provide such information as set forth in the applicable Research Plan. All other adverse event reports involving the Agent(s) shall be reported to the FDA consistent with 21 CFR § 312.32 and 312.33 and to the NCI and the Collaborator using the specified NCI Clinical Data Reporting system. The IND Sponsor will also be required to submit serious adverse event reports to CTEP AERS, as applicable.
2. IND Sponsor shall provide to Collaborator adverse events submitted to CTEP AERS or the specified NCI Clinical Data Reporting system by Approved Investigator(s) in its quarterly reports. As soon as the IND Sponsor receives a notification of an adverse event involving the Formulary Agent(s), but no later than one (1) working day, such notification will be reported using the CTEP AERS system.

(b) Collaborator shall ensure that the IND Sponsor and DCTD have the most current contact information for reporting adverse events to Collaborator. In the event that Collaborator informs the FDA of any serious and unexpected adverse events involving the Formulary Agent(s) that arise outside of the Protocol, Collaborator must notify the IND Sponsor and DCTD at the same time. NCI will ensure that the IND Sponsor will then notify the investigator(s) at the Clinical Research Sites, if appropriate.

4.5 **IND Annual Reports**. NCI shall ensure that the IND Sponsor will provide Collaborator a copy of the Annual Report following the submission of the Annual Report to the FDA. Collaborator agrees that Annual Reports will be kept confidential in accordance with Article 8.

**Article 5. Staffing, Financial, and Materials Obligations**

5.1 **NCI and Collaborator Contributions**. The contributions of any staff, funds, materials, and equipment by the Parties are set forth in Appendix A. The Federal Technology Transfer Act of 1986, 15 U.S.C. § 3710a(d)(1) prohibits NCI from providing funds to Collaborator for any activities under this CRADA.

**Article 6 and Article 7 are intentionally deleted in their entirety.**

**Article 8. Rights of Access and Publication**

8.1 **Right of Access to CRADA Data**. NCI (through Approved Investigators) and Collaborator agree to exchange all CRADA Data. If Collaborator possesses any human biological specimens (“Biospecimen”) from clinical trials under the CRADA, the Biospecimens must be handled as described in the Protocol and other agreements if applicable.

8.2 **Use of CRADA Data**. The Parties will be free to utilize CRADA Data internally for their own purposes, consistent with their obligations under this CRADA. Collaborator may share CRADA Data with any contractors, Affiliates, development partners or agents it has engaged to conduct the Research Plan on the Formulary Agents, provided the obligations of this Article 8.2 are simultaneously conveyed. Collaborator shall not transfer CRADA Data to any third party other than those set forth in this section without the written permission of the NCI. Following NCI’s permission, Collaborator may share data with such third party provided that the third party is bound by confidentiality terms at least as stringent as those set forth herein.

Collaborator and NCI will use reasonable efforts to keep CRADA Data confidential until published. To the extent permitted by law, each Party will have the right to use any and all CRADA Data in and for any regulatory filing by or on behalf of the Party.

8.3 **Confidential Information**. Each Party agrees to limit its disclosure of Confidential Information to the amount necessary to carry out a Study in accordance with the Research Plan or exercise its rights and obligations under this CRADA, and will reasonably place a confidentiality notice on all this information, or otherwise identify such information as confidential. A Party orally disclosing Confidential Information to the other Party will use commercially reasonable efforts to summarize the disclosure in writing and provide it to the other Party within fifteen (15) days of the disclosure. Each Party receiving Confidential Information agrees to use it only for the purposes described in the Research Plan. Either Party may object to the designation of information as Confidential Information by the other Party. Notwithstanding the foregoing, the failure to place notice, identify or otherwise summarize a disclosure as confidential shall not affect the confidential nature of such information if a reasonable person skilled in the industry applicable to this CRADA and the Research Plan under it would recognize such information as being confidential or proprietary.

8.4 **Protection of Confidential Information**. Confidential Information will not be disclosed, copied, reproduced or otherwise made available to any other person or entity without the consent of the owning or providing Party except as required by a court or administrative body of competent jurisdiction, or federal law or regulation. Each Party agrees to use reasonable efforts to maintain the confidentiality of Confidential Information, which will in no instance be less effort than the Party uses to protect its own Confidential Information. Each Party agrees that a Party receiving Confidential Information will not be liable for the disclosure of that portion of the Confidential Information which, after notice to and consultation with the disclosing Party, the receiving Party determines may not be lawfully withheld, provided the disclosing Party has been given a reasonable opportunity to seek a court order to enjoin disclosure.

8.5 **Human Subject Protection**. The clinical research to be conducted under this CRADA involves Human Subjects or human tissues within the meaning of 45 C.F.R. Part 46, and all research to be performed under this CRADA will conform to applicable federal laws and regulations. Additional information is available from the HHS Office for Human Research Protections (http://www.hhs.gov/ohrp/).

8.6 **Duration of Confidentiality Obligation**. The obligation to maintain the confidentiality of Confidential Information will expire at the earlier of the date when the information is no longer Confidential Information as defined in Article 2 or three (3) years after the expiration or termination date of this CRADA, except for IPI, for which the obligation to maintain confidentiality will extend indefinitely. Collaborator may request an extension to this term when necessary to protect Confidential Information relating to products not yet commercialized.

8.7 **Publication**. Subject to Section 8.2, above, the Parties are encouraged to make publicly available the results of their activities under the Research Plan. However, Collaborator will not publish or publicly disclose any CRADA Data provided by Approved Investigators under the CRADA without NCI’s or the Approved Investigator’s written permission. Before Approved Investigators submit a paper or abstract for publication about CRADA Data, Collaborator will have forty-five (45) days to review proposed manuscripts and seven (7) business days to review proposed abstracts to assure that its Confidential Information is protected. Collaborator may request in writing that a proposed publication be delayed for up to sixty (60) additional days as necessary to file a patent application. Manuscripts to be submitted for publication by Approved Investigators will be sent to NCI’s Regulatory Affairs Branch [NCICTEPpubs@mail.nih.gov] for forwarding to Collaborator for review as soon as they are received and in compliance with the timelines outlined above. Abstracts to be presented by Approved Investigators will be sent to NCI’s Regulatory Affairs Branch [NCICTEPpubs@mail.nih.gov] for forwarding to Collaborator as soon as they are received, preferably no less than seven (7) business days prior to submission, but prior to presentation or publication, to allow for preservation of U.S. or foreign patent rights.

8.8 **Clinical and Non-Clinical Investigators’ Research and Development Activities; Access to Raw Data**. Approved Investigator will be responsible for the conduct of the applicable Protocol or Proposal. The MTA between the NCI and Approved Investigators includes the Intellectual Property Option to Collaborator (including any updates) offering Collaborator first rights of negotiation to extramural Inventions

(web site: <http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm>).

8.8.1 NCI shall ensure that Approved Investigators agree to confidentiality provisions at least as restrictive as those provided in this CRADA and to Collaborator’s use of CRADA Data for obtaining regulatory approval for marketing Formulary Agent.

8.8.2 If Collaborator wants access to Raw Data or any other data in the possession of the Approved Investigators working with Agent, Collaborator will make arrangements directly with the Approved Investigators. Collaborator will bear any costs associated with Raw Data provided in formats customized for Collaborator, which costs will be paid by Collaborator directly to the Approved Investigators.

8.9 **Multi-Party Data Rights.** For clinical Protocol(s) where Formulary Agent is used in combination with another investigational agent supplied to NCI pursuant to another Formulary CRADA between NCI and an entity not a Party to this CRADA or another agreement between the institution that Approved Investigator is associated with and an entity not a Party to this CRADA (hereinafter referred to as “Third Party”), the access and use of Multi-Party Data by the Collaborator and Third Party shall be co-exclusive and reciprocal as follows:

8.9.1 NCI will provide both Collaborator and Third Party with notice regarding the existence and nature of the agreements governing their collaborations with NIH, and the design of the proposed combination Protocol(s),

8.9.2 Collaborator shall agree to permit use of the Multi-Party Data from these trials by Third Party to the extent necessary to allow Third Party to develop, obtain regulatory approval for, or commercialize its own investigational agent(s). However, this provision will not apply unless Third Party also agrees to Collaborator’s reciprocal use of Multi-Party Data.

8.10 **Access, review and receipt of Identifiable Private Information.** Collaborator access to and review of Identifiable Private Information shall be only for on-site quality auditing. Collaborator will receive Identifiable Private Information only if necessary for purposes of satisfying FDA or other health authorities' reporting requirements, and for internal research purposes, directly related to obtaining regulatory approval of Formulary Agent. Collaborator is prohibited from access, review, receipt, or use of such information for other purposes. NCI shall ensure through Approved Clinical Investigator of the Protocols that (a) all IRB approved Protocols and informed consent documents related to this research project will clearly describe this practice; (b)if the Collaborator will have access to Identifiable Private Information, the Protocol, including the informed consent must clearly state (i) the existence of the Collaborator; (ii) the Collaborator's access to Identifiable Private Information, if any; and (iii) the extent to which confidentiality will be maintained. For clinical Protocol(s) involving a third party, such party's access, review, receipt, or use of Identifiable Private Information shall be subject to the same limitations as described in this Article 8.10.

**Article 9. Representations and Warranties**

9.1 **Representations of NCI**. NCI hereby represents to Collaborator that:

9.1.1 NCI has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that NCI’s official signing this CRADA has authority to do so.

9.1.2 To the best of its knowledge and belief, neither NCI nor any of its personnel involved in this CRADA is presently subject to debarment or suspension by any agency of the Government that would directly affect its performance of the CRADA. Should NCI become aware that any of its personnel involved in this CRADA are debarred or suspended during the term of this CRADA, NCI will notify Collaborator within thirty (30) days.

9.2 **Representations and Warranties of Collaborator**. Collaborator hereby represents and warrants to NCI that:

9.2.1 Collaborator has the requisite power and authority to enter into this CRADA and to perform according to its terms, and that Collaborator’s official signing this CRADA has authority to do so.

9.2.2 Neither Collaborator nor any of its personnel involved in this CRADA, including Affiliates, agents, and contractors are presently subject to debarment or suspension by any agency of the Government. Should Collaborator become aware that any of its personnel involved in this CRADA are debarred or suspended during the term of this CRADA, Collaborator will notify NCI within thirty (30) days.

9.2.3 Subject to Paragraph 12.3, and if and to the extent Collaborator has agreed to provide funding under Appendix A, Collaborator is financially able to satisfy these obligations in a timely manner as agreed in the Research Plan.

9.2.4 The Formulary Agent provided has been produced in accordance with the FDA’s current Good Manufacturing Practice set out in 21 C.F.R. §§ 210-211, and ICH Q7, and meets the specifications cited in the Certificate of Analysis and Investigator’s Brochure provided, and as may be updated from time to time.

**Article 10. Expiration and Termination**

10.1 **Expiration**. This CRADA will expire on the last date of the term set forth on the Summary Page. In no case will the term of this CRADA extend beyond the term indicated on the Summary Page unless it is extended in writing in accordance with Paragraph 13.6.

10.2 **Termination by Mutual Consent**. NCI and Collaborator may terminate this CRADA at any time by mutual written consent.

10.3 **Unilateral Termination**. Either NCI or Collaborator may unilaterally terminate this CRADA at any time by providing a written notice at least sixty (60) days before the desired termination date. NCI may, at its option, retain funds transferred to NCI before unilateral termination by Collaborator for use in completing the Research Plan. If Collaborator terminates this Agreement before the completion of all approved or active Protocol(s), then Collaborator will supply enough Formulary Agent to complete these Protocol(s) unless termination is for safety concerns, lack of enrollment, or other mutually agreed reasons.

Collaborator may terminate the CRADA at its option and suspend supply of Formulary Agent if the Approved Investigators fails to meet patient accrual goals. Collaborator will inform Approved Investigators three (3) months prior to such a suspension and allow the Approved Investigator to take corrective action. If corrective action is met, Collaborator will be responsible for supplying sufficient Formulary Agent to complete the applicable Study, if corrective action is not met the Study may be terminated at Collaborator’s discretion.

10.4 **New Commitments**. Neither Party will incur new expenses related to this CRADA after expiration, mutual termination or a notice of a unilateral termination and will, to the extent feasible, cancel all outstanding commitments and contracts by the termination date. Collaborator acknowledges that NCI will have the authority to retain and expend any necessary funds for up to five (5) years subsequent to the expiration or termination date to cover any unpaid, undisputed costs obligated during the term of the CRADA in undertaking the activities set forth in the Research Plan in accordance with this CRADA.

 **Article 11. Disputes**

11.1 **Settlement**. Any dispute arising under this CRADA which is not disposed of by agreement of the NIH CRADA Extramural Investigator/Officer(s) and CRADA Collaborator PI(s) will be submitted jointly to the signatories of this CRADA. If the signatories, or their designees, are unable to jointly resolve the dispute within thirty (30) days after notification thereof, the Assistant Secretary for Health (or his/her designee or successor) will propose a resolution. Nothing in this Paragraph will prevent any Party from pursuing any additional administrative remedies that may be available and, after exhaustion of such administrative remedies, pursuing all available judicial remedies.

11.2 **Continuation of Work**. Pending the resolution of any dispute or claim pursuant to this Article 11, the Parties agree that performance of all obligations will be pursued diligently.

**Article 12. Liability**

12.1 **NO WARRANTIES**. EXCEPT AS SPECIFICALLY STATED IN ARTICLE 9, THE PARTIES MAKE NO EXPRESS OR IMPLIED WARRANTY AS TO ANY MATTER WHATSOEVER, INCLUDING THE CONDITIONS OF THE RESEARCH OR ANY INVENTION OR MATERIAL, WHETHER TANGIBLE OR INTANGIBLE, MADE OR DEVELOPED UNDER OR OUTSIDE THE SCOPE OF THIS CRADA, OR THE OWNERSHIP, MERCHANTABILITY, OR FITNESS FOR A PARTICULAR PURPOSE OF THE RESEARCH OR ANY INVENTION OR MATERIAL, OR THAT A TECHNOLOGY UTILIZED BY A PARTY IN THE PERFORMANCE OF THE RESEARCH PLAN DOES NOT INFRINGE ANY THIRD-PARTY PATENT RIGHTS.

12.2 **Indemnification and Liability**. Collaborator agrees to hold the Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of the use by Collaborator for any purpose of the CRADA Data, unless due to the negligence or willful misconduct of NCI, its employees, or agents. The Government has no statutory authority to indemnify Collaborator. Each Party otherwise will be liable for any claims or damages it incurs in connection with this CRADA unless due to the gross negligence or willful misconduct of the othe Party, except that NCI, as an agency of the Government, assumes liability only to the extent provided under the Federal Tort Claims Act, 28 U.S.C. Chapter 171.

12.3 ***Force Majeure***. Neither Party will be liable for any unforeseeable event beyond its reasonable control and not caused by its own fault or negligence, which causes the Party to be unable to perform its obligations under this CRADA, and which it has been unable to overcome by the exercise of due diligence. If a *force majeure* event occurs, the Party unable to perform will promptly notify the other Party. It will use its best efforts to resume performance as quickly as possible and will suspend performance only for such period of time as is necessary as a result of the *force majeure* event.

**Article 13. Miscellaneous**

13.1 **Governing Law**. The construction, validity, performance and effect of this CRADA will be governed by U.S. federal law, as applied by the federal courts in the District of Columbia. If any provision in this CRADA conflicts with or is inconsistent with any U.S. federal law or regulation, then the U.S. federal law or regulation will preempt that provision.

13.2 **Compliance with Law**. IC and Collaborator agree that they will comply with, and advise any contractors, Approved Investigators, or agents they have engaged to conduct the Research Plan to comply with, all applicable Executive Orders, statutes, and HHS regulations relating to research on human subjects (45 C.F.R. Part 46, 21 C.F.R. Parts 50 and 56) and relating to the appropriate care and use of laboratory animals (7 U.S.C. §§ 2131 *et seq*.; 9 C.F.R. Part 1, Subchapter A). IC and Collaborator will advise any contractors, Approved Investigators, or agents they have engaged to conduct clinical trials for this CRADA that they must comply with all applicable federal regulations for the protection of Human Subjects, which may include the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164 and Corporate Integrity Policy. Collaborator agrees to ensure that its employees, contractors, and agents who might have access to a “select agent or toxin” (as that term is defined in 42 C.F.R. §§ 73.4-73.5) transferred from IC is properly licensed to receive the “select agent or toxin.”

13.3 **Waivers**. None of the provisions of this CRADA will be considered waived by any Party unless a waiver is given in writing to the other Party. The failure of a Party to insist upon strict performance of any of the terms and conditions hereof, or failure or delay to exercise any rights provided herein or by law, will not be deemed a waiver of any rights of any Party.

13.4 **Headings**. Titles and headings of the articles and paragraphs of this CRADA are for convenient reference only, do not form a part of this CRADA, and will in no way affect its interpretation.

13.5 **Severability**. The illegality or invalidity of any provisions of this CRADA will not impair, affect, or invalidate the other provisions of this CRADA.

13.6 **Amendments**. No change to this CRADA other than the addition of clinical studies or additional Formulary Agent(s) to the CRADA Research Plan, may be made without mutual, written agreement by both Parties.

13.7 **Assignment**. Neither this CRADA nor any rights or obligations of any Party hereunder shall be assigned or otherwise transferred by either Party without the prior written consent of the other Party. The Collaborator acknowledges the applicability of 41 U.S.C. § 15, the Anti Assignment Act, to this Agreement.  The Parties agree that the identity of the Collaborator is material to the performance of this CRADA and that the duties under this CRADA are nondelegable.

13.8 **Notices**. All notices pertaining to or required by this CRADA will be in writing, signed by an authorized representative of the notifying Party, and delivered by first class, registered, or certified mail, or by an express/overnight commercial delivery service, prepaid and properly addressed to the other Party at the address designated on the Contacts Information Page, or to any other address designated in writing by the other Party. Notices will be considered timely if received on or before the established deadline date or sent on or before the deadline date as verifiable by U.S. Postal Service postmark or dated receipt from a commercial carrier. Either Party may change its address by notice given to the other Party in the manner set forth above.

13.9 **Independent Contractors**. The relationship of the Parties to this CRADA is that of independent contractors and not agents of each other or joint venturers or partners. Each Party will maintain sole and exclusive control over its personnel and operations. If Collaborator elects to perform any portion of the Research Plan through a contractor(s) or consultant(s), Collaborator agrees to incorporate into such contract all provisions necessary to ensure that the work of such contractor(s) or consultant(s) is governed by the terms of the CRADA, including, but not limited to a provision for the assignment of inventions of the contractor(s) or consultant(s) to the Collaborator.

13.10 **Use of Name; Press Releases**. By entering into this CRADA, the Government does not directly or indirectly endorse any product or service that is or will be provided, whether directly or indirectly related to either this CRADA or to any patent or other intellectual-property license or agreement that implements this CRADA by Collaborator, its successors, assignees, or licensees. Collaborator will not in any way state or imply that the Government or any of its organizational units or employees endorses any product or services. Each Party agrees to provide proposed press releases that reference or rely upon the work under this CRADA to the other Party for review and comment at least five (5) business days before publication. Subject to the review process of abstracts in Section 8.7, either Party may disclose the Summary Page of the CRADA to the public without the approval of the other Party.

13.11 **Reasonable Consent**. Whenever a Party’s consent or permission is required under this CRADA, its consent or permission will not be unreasonably withheld.

13.12 **Export Controls**. Collaborator agrees to comply with U.S. export law and regulations, including 21 U.S.C. 382 and 21 CFR Part 312.110. If Collaborator has a need to transfer IC’s Confidential Information to a person located in a country other than the United States, to an Affiliate organized under the laws of a country other than the United States, or to an employee of Collaborator in the United States who is not a citizen or permanent resident of the United States, Collaborator will acquire any and all necessary export licenses and other appropriate authorizations.

13.13 **Entire Agreement**. This CRADA, and the documents referenced within or attached hereto as an appendix, constitutes the entire agreement between the Parties concerning the subject matter of this CRADA and supersedes any prior understanding or written or oral agreement.

13.14 **Survivability**. The provisions of Paragraphs 3.6, 4.2, 4.3, 4.4, 8.1-9.2, 10.3-10.4, 11.1, 11.2, 12.1-12.3, 13.1-13.3, 13.7, 13.8, 13.10 and 13.14 will survive the expiration or early termination of this CRADA.

 SIGNATURES BEGIN ON THE NEXT PAGE

 SIGNATURE PAGE

**ACCEPTED AND AGREED**

By executing this agreement, each Party represents that all statements made herein are true, complete, and accurate to the best of its knowledge. Collaborator acknowledges that it may be subject to criminal, civil, or administrative penalties for knowingly making a false, fictitious, or fraudulent statement or claim.

FOR NCI:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_

James H. Doroshow, M.D. Date

Deputy Director, National Cancer Institute

FOR COLLABORATOR:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_

Signature Date

Typed Name:

Title:

 CONTACTS INFORMATION PAGE

**CRADA Notices**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| Jianqiao Zhang, PhDAssociate Chief, Agreement Coordination GroupRegulatory Affairs BranchDivision of Cancer Treatment and DiagnosisNational Cancer InstituteEmail: zhangjia@mail.nih.govTel: (240) 276-6580 |  |

 **Delivery of Materials Identified In Appendix B (if any)**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| N/A | N/A |

**Formulary Agent Delivery**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| Mr. Charles HallPharmaceutical ManagementBranch, CTEP, DCTD, NCI9609 Medical Center Drive, Rm 5W240Rockville, MD 20892-9704Tel: (240) 276-6575 | Name:Address:Tel: |

e-mail: hallch@mail.nih.gov

**Investigator’s Brochure**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| IB Coordinator,Pharmaceutical Management Branch, CTEP, DCTD, NCI9609 Medical Center Drive, Rm 5W240Rockville, MD 20892-9704Tel: (240) 276-6575 | Name:Address:Tel: |

e-mail: IBCoordinator@mail.nih.gov

**Review of Manuscripts and Abstracts**

For NCI: For Collaborator:

|  |  |
| --- | --- |
| NCICTEPpubs@mail.nih.gov |  e-mail:  |

**Adverse Events, Safety Reports**

For NCI: For Collaborator:

CTEPSupportAE@tech-res.com

**Protocols, Proposals, LOIs**

For NCI: For Collaborator:

CTEPprotcolcomments@tech-res.com

SUMMARY PAGE

*EITHER PARTY MAY, WITHOUT FURTHER CONSULTATION OR PERMISSION,*

*RELEASE THIS SUMMARY PAGE TO THE PUBLIC.*

TITLE OF CRADA:

PHS [IC] Component: National Cancer Institute

NIH CRADA Extramural Investigator/Officer: Dr. Jeffrey Moscow/Dr. Margaret Mooney

Collaborator:

CRADA Collaborator Principal Investigator:

Term of CRADA: five (5) years from the Effective Date

 ABSTRACT OF THE RESEARCH PLAN:

Collaborator and the National Cancer Institute have entered into a Cooperative Research and Development Agreement (“CRADA”) to support the Cancer Moonshot initiative. Under the CRADA DCTD will distribute Collaborator’s anti-cancer agent(s) provided to the NCI Formulary to investigators to conduct investigator-initiated clinical trials.