# PUBLIC HEALTH SERVICE
## EXTRAMURAL
## CLINICAL TRIAL AGREEMENT

This Clinical Trial Agreement, hereinafter referred to as the "CTA," consists of this Cover Page, an attached Agreement, a Signature Page and various Appendices referenced in the Agreement. This Cover Page serves to identify the Parties to this CTA:

(1) The **National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, (NIDDK)**, hereinafter referred to as "**NIDDK**", and

(2) _____ , having offices at _____ hereinafter referred to as "**Collaborator**".

**Background**

The NIDDK recognizes the importance of the pharmaceutical industry in the clinical development of new methods of treatment of many ***[insert disease or disorder]*** diseases and conditions. NIDDK wishes to foster collaboration with industry whenever possible. As part of its mission to improve the treatment of ***[insert disease or disorder]*** diseases, NIDDK shares with industry the important goal of defining the contribution of pharmacologic agents in the treatment of ***[insert disease or disorder]***. The NIDDK, therefore, recognizes and supports the need of private sponsors to focus at the appropriate time on clinical trials focused on the treatment of ***[insert disease or disorder].***

Thus, the NIDDK considers it appropriate for the investigators funded by the NIDDK to conduct a clinical trial that, in part, is supported by pharmaceutical firms, provided that the trial has scientific merit and is consistent with the overall goals of the funded investigators and the NIDDK.

The pharmaceutical firms recognize that participation in clinical trials developed by NIDDK funded investigators can lead to further insights into the indications for utilization of their drugs in the treatment of ***[insert disease or disorder].*** The pharmaceutical firms also recognize the necessity of preserving the spirit of free and open inquiry among clinical investigators.

Collaborator is considered to be exempt from 45 CFR Part 46 and consequently Collaborator does not need an Assurance number from the Office of Human Research Protections, at the NIH for the following reasons:

1. Collaborator employees or agents neither interact or intervene with living individuals nor obtain, receive, or possess Identifiable Private Information about living individuals (e.g., Collaborator employees will receive and/or analyze data that cannot be linked to individual subjects, either directly or indirectly through codes).
2. Collaborator employees or agents access or review of Identifiable Private Information will be solely for purposes of on-site quality auditing. This Agreement unequivocally prohibits use or release of such information for other purposes.

WHEREAS, NIDDK, through its Project Scientist(s), [names], wishes to conduct a clinical trial that will involve the use of [*name specific Study Drug to be supplied under this agreement*] supplied by Collaborator, upon terms and conditions set forth in this Agreement. NOW, THEREFORE, the parties agree to the following:

## AGREEMENT

### Article 1. Definitions

As used in this CTA, the following terms shall have the indicated meanings:

1.1 "**Adverse Event Reaction**" or AER means an adverse clinical experience as defined under 21 CFR § 310.305 "Records and Reports Concerning Adverse Drug Experience", and other applicable Federal Regulations. Specific guidelines and policies for reporting adverse drug reactions, as well as common toxicity criteria have been developed. A Serious Adverse experience shall include any experience which results in death, persistent or substantial disability, in-patient hospitalization or prolongation of hospitalization, is immediately life-threatening or is a cancer, congenital anomaly or overdose. Also other important medical events that may not result in death, not be life-threatening, or not require hospitalization, may be considered serious adverse experiences when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical/surgical intervention to prevent one of the other outcomes. An adverse experience which is "serious" and is related to use of study therapy shall be reported to the Collaborator and to the FDA in accordance with 21 CFR 312.32 and 314.80.

1.2 "**Annual Report**" means an Annual Report which is a report of the progress of an IND associated investigation which the NIDDK is required to submit to the FDA within 60 days of the anniversary date that the IND went into effect (pursuant to 21 C.F.R. § 312.33). If NIDDK is the drug sponsor, NIDDK shall provide COLLABORATOR a copy of the Annual Report simultaneously with the submission of the Annual Report to the FDA. In accordance with NIDDK procedures, Annual Reports will not be made public

1.3 "**Clinical Center**" means a grantee institution that will conduct or perform experimental, developmental, or research work and has executed a Funding Agreement.

1.4 "**Confidential Information**" means data or information related to the uses of ***[insert study drug]*** disclosed by either Party to the other Party. All such Confidential Information shall be owned solely by the providing Party. Confidential Information shall not include:

(a) data or information that is in the public domain or subsequently enters the public domain through no fault of the receiving Party; or

(b) data or information that is presently known or becomes known to the receiving Party from its own independent sources from a person having the legal right to disclose data; or

(c) data or information that is developed independently by individuals who have not had access to Confidential Information; or

(d) data or information that is required to be disclosed by law.

Regarding any particular subset of Confidential Information, if any one or more of the above provisions of this definition is met during the term of this Agreement, the relevant information shall no longer be considered Proprietary Information.

1.5 "**Cooperative Group**" means the cooperative group composed of investigators who join together to develop and implement common protocols (as the protocols approved by the Steering Committee, and mutually agreed to by NIDDK). The distinguishing characteristic of cooperative groups is the central operations and statistical offices that support the administrative requirements of the research and perform central data collection and analysis. Protocol compliance of cooperative groups is verified by each group through its own quality assurance program and through site visit auditing coordinated by a Data Coordinating Center as defined in the approved protocol for the clinical trial.

1.6 "**Data Coordinating Center**" or **"DCC**" means a non-governmental organization funded by NIDDK specifically for this clinical trial to receive, review, and perform data management tasks on the individual patient case report forms completed for this Study. On-site audits are performed by the DCC as specified in the clinical trial protocol to assess data verification, protocol compliance, adherence to regulatory requirements.

1.7 **"Drug Master Files"** or **"(DMFs)"** means reference files submitted to FDA that are used in the review of investigational and marketing applications for human drugs. Drug Master Files are submitted to the FDA to allow another party to reference this material without disclosing to that party the contents of the file.

1.8 **"Data and Safety Monitoring Board**" means a committee, appointed and established by the NIDDK, composed of individuals not affiliated with any of the institutions in the cooperative agreement. The Board serves as external reviewers of the trial and advisors to the NIDDK and the Steering Committee. The principal responsibility is to monitor the emerging results of the trial to assess treatment effectiveness, and participant safety. The Chair of the Steering Committee, the NIDDK Project Scientists and the staff of the DCC are ex-officio members of the Board.

1.9 "**FDA**" means the Food and Drug Administration, PHS.

1.10 "**Funding Agreement**" means a Contract, Grant, or Cooperative Agreement entered into between a Federal agency and another party for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government. Pertinent statutes include: 31 U.S.C. §§ 6303-6305; 35 U.S.C. §§ 200-212; and any and all implementing regulations thereof.

1.11 "**Grant**" means a funding agreement that is an award of financial assistance which may be provided for support of basic research in a specific field of interest to the funding Federal agency. Generally, awarding grants are pursuant to statutory authorities contained in Section 301(a) and 487 of the PHS Act, as amended (42 USC 241a and 42 USC 288).

1.12 **"Human Subjects"** means individuals whose physiologic or behavioral characteristics and responses are the object of study in a research project. Under the federal regulations for the protection of human subjects, human subjects are defined as living individuals about whom an investigator conducting research obtains: (1) data through intervention or interaction with the individual; or (2) identifiable private information (45 CFR §46.102(f)).

1.13 **"Identifiable Private Information"** means patient-identifying data from medical records or attached to patient specimens, to be obtained prospectively or from stored medical records or specimens, that can be linked to individual human subjects, either directly or indirectly through codes.

1.14 "**IND**" means an Investigational New Drug Application that is the legal mechanism under which experimental new-drug research is performed in the United States and is submitted to the FDA to receive approval to conduct experimental clinical trials. The FDA regulations require continual updates to the IND including, but not limited to, Annual Reports, Adverse Event Reaction reports, new protocols, protocol amendments and pharmaceutical data.

1.15 **"Investigational Drug Brochure" or "IDB"** means a document containing all the relevant information about the drug, including animal screening, pre-clinical toxicology, and detailed pharmaceutical data. Also included, if available is a summary of current knowledge about pharmacology and mechanism of action and a full description of the clinical toxicities.

1.16 "**Investigator**" means any physician who assumes full responsibility for the treatment and evaluation of patients on research protocols as well as the integrity of the research data.

1.17 "**NIDDK**" means the National Institute of Diabetes and Digestive and Kidney Diseases, an institute of the National Institutes of Health and a Federal Agency of the Department of Health and Human Services.

1.18 "**NIH**" means the National Institutes of Health, Public Health Service, DHHS.

1.19 "**Parties**" means Collaborators and the NIDDK.

1.20 "**PHS**" means the Public Health Service.

1.21 "**Principal Investigator**" **or "PI**" means a physician who has organizational and fiscal responsibility for the use of federal funds to conduct a plan of research.

1.22 "**Project Scientist**" means the individual whose responsibilities include oversight of the activities of a government contract or cooperative agreement.

1.23 **"Protocol"** means the document describing how the clinical trial is to be performed.

1.24 "**Steering Committee**" the committee consisting of the Principal Investigators of each funded Clinical Center in the Cooperative Group, and representatives from the **NIDDK**. Subcommittees of the steering committee will be designated by the Committee Chairperson. These committees may include: Publications, Clinical Review, Protocol.. The subcommittees will consist of both voting and non-voting members selected from the Steering Committee.

1.25 "**Study**" means the specific clinical trial for which this Agreement is prepared. Clinical Protocol entitled ***[insert Protocol name]*** is attached as Appendix A.

1.26 "**Study Drug"** means ***[insert drug identification].***

1.27 **"Raw Data"** means the primary quantitative and empirical data first collected by an Investigator from experiments and clinical trials conducted under the scope of this Agreement.

1.28 **"Summary Data"** means a summary of the Raw Data used to prepare an Annual Report to the FDA. Summary Data shall specifically exclude Identifiable Private Information.

**Article 2. Investigational New Drug Applications**

Generally, the needs of both NIDDK and the Collaborator are best served when each sponsors an IND. It is expected, therefore, that either NIDDK or Collaborator will submit an IND that may cross-reference an IND, Drug Master File, or New Drug Application held by the other. In the event NIDDK elects to file its own IND, the Collaborator agrees to provide NIDDK background data and information and agrees to execute such documents as may be reasonably required to effect such cross-reference. Collaborator's employees will be reasonably available to respond to inquiries from the FDA regarding information or data contained in NIDDK's IND, Drug Master File, New Drug Application, or other information and data provided to NIDDK by Collaborator pursuant to this Article 2. Nothing herein shall require Collaborator to undertake additional studies of any kind or to prepare and submit any additional data to the FDA that are not already included in NIDDK's IND, Drug Master File, or New Drug Applications. In the event that either Party supplies CONFIDENTIAL information directly to the other Party in support of an IND, such information will be protected in accordance with the corresponding Confidentiality provisions of Article 10 of this Agreement. All information will be fully shared from each IND including, but not limited to, Investigation Drug Brochures, Adverse Event Reactions, and formulation and pre-clinical data, including toxicology findings. However, certain Collaborator proprietary information pertaining to manufacturing processes that is not required for the conduct of the Study may be held in confidence by Collaborator and not disclosed to NIDDK.

Collaborator may sponsor its own clinical trials and hold its own IND for studies performed outside the scope of this Study from which all data is proprietary Collaborator for purposes of this Agreement.

**Article 3. Institutional Review Board Review**

Before the Study is initiated, the NIDDK shall obtain from the participating Institutional Review Boards (IRB's) of each participating Clinical Center, evidence of review and approval of the Study and the patient informed consent form to be used at that Center. The Study's DCC will serve as a repository for IRB approved protocols and patient consent forms, including the yearly renewals. The DCC will monitor the receipt of informed consent from all Study participants.

**Article 4. Protocol**

The Study will be conducted in accordance with the Protocol and all amendments as established by the PI through the Steering and Planning committee of the Cooperative Group. The Study is projected to enroll and treat approximately ***[insert number]*** patients in the United States for a minimum of four (4) years and a maximum of six (6) years.

**Article 5. Conduct Of Study**

The Study shall be conducted in accordance with the terms of this Agreement, the Protocol(s), and all applicable federal laws, regulations, and guidelines. The location(s) where the Study is to be conducted and the number of patients to be enrolled in the Study are set forth in the Protocol(s).

**Article 6. Adverse Event Reactions, Annual Reports, Other IND Data**

NIDDK will provide COLLABORATOR with copies of all Adverse Event Reactions that may be possibly, probably, or definitely related to the use of the Study Drug used in this Study concurrently with their submission to FDA. In addition, copies of the Annual Reports and other pertinent IND data will be provided to COLLABORATOR by NIDDK as they become available. During the course of this Agreement,

Collaborator in turn will provide the PI and NIDDK with relevant Adverse Event Reaction information from any related on-going trials related to the Study Drug.

**Article 7. Drug Information and Supply**

For the performance of this Study, Collaborator shall supply the Study Drug and matching placebo, without charge. Study Drug shall be supplied on such schedule as specified by the DCC. Further, neither NIDDK nor Principal Investigator shall charge any third party payer or patient enrolled in the Study for the Study Drug, nor shall NIDDK or Principal Investigator include the cost of such drug in any cost report to third party payers.

(a) Collaborator will provide sufficient Study Drug and placebo to complete the Study in accordance with the Protocol.

(b) Collaborator will provide starter kits, drug maintenance and placebo in sufficient quantity for the patients participating in the Study.

(c) All Collaborator drug supplies will be packaged and shipped by Collaborator to the Drug Distribution Center (DDC) funded by the NIDDK through the DCC. The drugs are then dispensed by the DDC to the individual hospital pharmacies at each participating Clinical Center. The Clinical Center pharmacies will dispense the assigned drugs to the Study participants in accordance with FDA regulations and the Study Protocol. Unused Study Drug will be returned to the DDC. The DDC will return unused Study Drug to Collaborator. Unused Study Drug shall be accounted for and disposed of in accordance with 21 CFR 312.59 and other applicable regulations.

(d) Re-supply of Study Drug by Collaborator will be based on the actual enrollment and treatment progress of the individual investigative sites.

(e) The Study Drug will not, under any circumstances, be used other than as specified in the Protocol.

(f) In the event that Collaborator shall abandon the trial at all sites prior to completion of Protocol, for any reason except for reasons of safety NIDDK shall have the right to continue to use the Study Drug for the purpose of allowing NIDDK to complete the Protocol of already enrolled patients.

Collaborator agrees to provide the NIDDK Principal Investigator with an Investigational Drug Brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the Study Drug. If such information is revised while the Study is in progress, the latest revisions will also be sent to the NIDDK Principal Investigator at that time.

For inquiries related to Study Drug, the contact person for Collaborator will be ***[insert contact info]*** and the NIDDK contacts will be Judith Starling, R.Ph, Investigational Drug Pharmacist (301-402-8139).

## Article 8. Data Rights

In the performance of this Clinical Trial Agreement, NIDDK may use Extramural Investigators for part or all of the completion of this Protocol through either Federal Grants or Federal Contracts. However, Extramural Investigators are not Parties to this Clinical Trial Agreement.

In addition to any other reports or data made available to them hereunder, Collaborator will be provided copies of all final Summary Data reports generated in connection with the use of Study Drug under this Agreement that are in the possession and control of NIDDK. Summary Data will be made fully available to Collaborator for regulatory purposes. The Raw Data generated under this Agreement are considered the property of the Party that generates the data. Analysis of the Raw Data will be conducted by DCC in accordance to the statistical methods delineated in the Protocol.

Collaborator will receive Identifiable Private Information only if necessary for purposes of satisfying FDA or health authorities' reporting requirements, and for internal research purposes directly related to obtaining regulatory approval of Study Drug.

## Article 9. Multi-Party Data

In accordance with the Protocol, in the event that the Study Drug will be used in combination with another compound(s), that is proprietary to an entity not a Party to this Clinical Trial Agreement (hereinafter referred to as Second Party), the access and use of data derived from such combination studies, (hereinafter referred to as Multi-Party Data), by the Collaborator and Second Party shall be co-exclusive as follows:

(a) NIDDK will provide all Parties with notice regarding the existence and nature of any agreements governing their use of Study Drug including, the design of the proposed combination protocol and the existence of any obligations that might restrict NIDDK's participation in the proposed combination protocols.

(b) Collaborator agrees to permit use of the Multi-Party Data from these trials by the Second Party to the extent necessary to allow said Second Party to develop, obtain regulatory approval or commercialize its own proprietary compound. However, this provision will not apply unless said Second Party also agrees to Collaborator's reciprocal use of Multi-Party Data.

(c) Collaborator and Second Party must agree in writing prior to the commencement of the combination trials that each will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own proprietary compound(s).

## Article 10. FDA Meeting

All meetings with FDA concerning this Study will be discussed by the Parties in advance and will be held on mutually agreed upon dates. Each Party will have the opportunity to suggest topics for the agenda for such a meeting and attend such meeting.

**Article 11. Confidential Information**

Upon completion or early termination of the Agreement, each Party will promptly return to the other Party all written Confidential Information supplied by or which incorporates Confidential Information of the other Party. Each Party will maintain one copy of the written Confidential Information supplied by or which incorporate Confidential Information from the other Party for archival purposes.

Neither Party will use any Confidential Information supplied by the other Party for its own benefit or for the benefit of any third party, and will not furnish to any third party any materials which incorporate any Confidential Information supplied by the other Party except as required under court order or the Freedom of Information Act (5 U.S.C. §552), or as otherwise required by law. The Parties shall immediately notify the other, in writing, of such required disclosure. All obligations of confidentiality and non-disclosure set forth in this Agreement will survive until the third (3rd) anniversary of the date on which this Agreement executed, unless extended by mutual written agreement.

**Article 12. Publications**

Collaborator-issued press releases that reference or rely upon the work of NIDDK under this Agreement shall be made available to NIDDK at least fourteen (14) days prior to publication for review and comments. Collaborator shall not in any way state or imply that this Agreement is in an endorsement of any product or service by the U.S. Government or any of its organizations units or employees.

Before NIDDK submits a paper or abstract for publication or otherwise intends to publicly disclose information about this Agreement, the Collaborator shall be provided thirty (30) days to review the proposed publication and seven (7) days prior to an abstract presentation, for review and comments or disclosure to assure that Proprietary or Confidential Information is protected.

The publication or other disclosure shall be delayed for up to thirty (30) additional days for publications and five (5) days for abstracts, upon written request by any Party as necessary to preserve U.S. or foreign patent or other intellectual property rights.

**Article 13. Patent Rights**

This CTA shall have no effect on the parties' rights in the existing inventions and technologies of each, including, but not limited to, the Study Drugs, and information and technology relating to the Protocol.

This Agreement does not represent a Cooperative Research and Development Agreement (CRADA under the Federal Technology Transfer Act, 15 U.S.C. 3701 et seq). Neither Party is authorized to promise rights in advance for inventions developed under this Agreement. Nothing in this Agreement will be construed as granting any license or obligation to license any intellectual property owned by Collaborator to NIDDK with respect to Study Drug other than the limited right to use Study Drug for the performance of the protocol in accordance with the terms of this Agreement.

**Article 14. Liability**

No indemnification for any loss, claim, damage, or liability is intended or provided by any Party under this agreement. Each Party shall be liable for any loss, claim, damage, or liability that said Party incurs as a result of its activities under this agreement, except that the NIDDK, as an agency of the United States, assumes liability only to the extent as provided under the Federal Tort Claims Act. (28 U.S.C. § 2571 et seq.)

**Article 15. Governing Law**

This Agreement shall be governed by and construed in accordance with Federal law as construed by the Federal Courts of the District of Columbia. Federal law and regulations will preempt any conflicting or inconsistent provisions in this Agreement. NIDDK and Collaborator, if Collaborator is sponsoring trials at the NIH under this Agreement, shall comply with all Department of Health and Human Services regulations relating to Human Subject use.

**Article 16. Period of Agreement**

The Agreement will be effective upon the execution of this document by all Parties and shall be in effect for ten (10) years from execution or five (5) years from enrollment of the last patient, whichever occurs first.

**Article 17. Notices**

If any party is required, or wishes to give any notice hereunder, such notice shall be deemed to be duly given when delivered via traceable courier to the address given in this Article by the addressee or by subsequent written notice to all parties. The primary executive contacts responsible for the coordination and communication of any written notices of this agreement are listed below:

For the NIDDK:

Name:
Title:
Address:

Telephone:
Fax:

With copy to:

Rochelle S. Blaustein, J.D.
Director, Technology Transfer and Development
12 South Dr, Room 3011, MSC 5632
Bethesda, MD 20892-5632
Telephone: 301-451-3636
Facsimile: 301-402-7461

For Collaborator:

Name:
Title:
Address:

Telephone:
Fax:

**Article 18. Modifications**

Upon mutual agreement of both parties, this Agreement may be amended as necessary to ensure the Agreement accurately reflects the terms and scope of the collaborative effort. All amendments must be in writing and signed by authorized representatives of both parties. Neither this Agreement 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, except that Collaborator may assign this Agreement to any of its parent, subsidiary or affiliate corporations or to a purchaser of the assets of its business to which this Agreement pertains without first obtaining the express written consent of the other party hereto. This Agreement shall be binding upon, and shall inure to the benefit of Collaborator, its successor and assigns.

**Article 19. Debarment Clause**

Each Party represents that to the best of its knowledge that it does not use in any capacity the services of any person debarred under subsections 306(A) or 306(B) of the Generic Drug Enforcement Act of 1992 (the "Act") in connection with any of the services performed by the Party hereunder. Each Party to the best of its knowledge will not use in any capacity the services of any person debarred under such subsection of the Act and will immediately disclose in writing to the other Party if any person who is performing services hereunder is debarred or if any action, suit, claim, investigation or legal or administrative proceeding is pending or, to the best of the Party's knowledge, threatened, relating to the debarment of the Party or any person performing services hereunder. Upon receipt of such written disclosure, or if the Party becomes aware of such debarment or threatened debarment, then the Party shall have the right to immediately terminate this Agreement.

**Article 20. Compliance with the Law**

NIDDK shall conduct the Study in accordance with all rules and regulations promulgated by the FDA, including 21 CFR Part 312, and all other applicable federal, state and local laws, rules and regulations.

**Article 21. Termination**

This Agreement may be terminated at any time by the mutual written consent of the Parties. Either Party may unilaterally terminate this Agreement at any time by giving written notice to the other Party at least ninety (90) days prior to the desired termination date subject to Article 21. Collaborator may terminate this Agreement immediately for safety reasons.

**Article 22. Alternative Sources of Study Drug in the Event Collaborator Terminates Development of the Study Drug**

In the event Collaborator elects to terminate its development of Study Drug for reasons other than safety, without the transfer of its development efforts and obligations under this Agreement to another party acceptable to NIDDK within ninety (90) days of discontinuation then Collaborator will provide NIDDK with Study Drug for all then-enrolled patients sufficient to complete the Study in the manner described in the Protocol.

Collaborator hereby grants to NIDDK a nonexclusive, nontransferable, irrevocable, paid-up license to practice or have practiced for or on behalf of the United States any invention which Collaborator may have or obtain on Study Drug, its manufacture, or on the process for use of Study Drug, throughout the world, for medical research purposes related to Delta Hepatitis. This license shall only become effective in the event Collaborator terminates its development of Study Drug for reasons other than safety, without the transfer of its development

efforts to another party within ninety (90) days of termination, and NIDDK elects to continue the development of Study Drug. This provision shall become null and void upon FDA approval of the Study Drug indications and marketing of the Study Drug by Collaborator.

**Article 23. Survivability**

The terms of this Agreement concerning supply of Drug, Identifiable Private Information, Data Rights, Confidential Information, Publications, Intellectual Property and Governing Law shall survive expiration or termination of this Agreement.

***SIGNATURES BEGIN ON FOLLOWING PAGE***

**FOR NIDDK:**

_____ _____

Griffin Rodgers, M.D. Date
Deputy Director

Mailing Address for Notices:

National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Building 31, Room 9A-52
9000 Rockville Pike
Bethesda, MD 20892

**FOR COLLABORATOR:**

_____ _____

Name: Date
Title:

Mailing Address for Notices: