Request for Proposals (RFP) on Phase I/II Clinical Trials for Bespoke AAV Gene Therapies to Treat Rare Diseases for the Accelerating Medicines Partnership® (AMP®) Bespoke Gene Therapy Consortium (BGTC)

A. FNIH RFP NUMBER: 2022-BGTC-005	**B. DATE ISSUED:** July 12, 2022	
C. ISSUED BY:	**D. ADDRESS OFFERS TO:**	
FNIH 11400 Rockville Pike Suite 600 Bethesda, MD 20852	**D.1. HARD COPIES (if required):** Electronic Submissions Only	**D.2. ELECTRONIC COPIES:** By email or secure file transfer (See Section VI for additional information)
E. FOR INFORMATION REGARDING THIS SOLICITATION CONTACT:		
E.1. NAME: Brad Garrison	**E.2. EMAIL bgarrison@fnih.org**	
IMPORTANT: **F.** To be considered for award, Offers must be received at the location specified in Block E.2. above by 11:59PM EST October 31, 2022. Offers must be clearly identified with the solicitation number provided in Block A above.		

Purpose

In December 2021, the Foundation for the National Institutes of Health (FNIH), in association with various National Institutes of Health (NIH) and private-sector partners, solicited nominations for rare diseases and disorders to be included in the BGTC's clinical program. Following review, a list of candidate diseases was developed (Table 1). The overall goal for this RFP is to solicit proposals for Phase I/II human Clinical Trials for the candidate indications listed in Table 1 below. The NIH will serve as the IND holder/regulatory sponsor of the clinical trials and have ultimate responsibility for research project direction, progress and oversight. The BGTC will engage BGTC partners, Contract Manufacturing Organizations (CMOs) and other manufacturing entities as needed to produce the Gene Therapy product and execute the IND-enabling Good Laboratory Practice (GLP) toxicity studies. The BGTC strongly encourages collaboration among researchers, academic institutions, and patient advocacy groups involved in the listed disease states.

Disease Name (pseudonym)	Affected Gene	BGTC Classification
Congenital Hereditary Endothelial Dystrophy (CHED)	SLC4A11	Eye / Cornea
MPS VI corneal disease	ARSB	Eye / Cornea
Leber Congenital Amaurosis 16 (LCA16)	KCNJ13	Eye / Retina
Retinitis pigmentosa (RP) - CNGB1	CNGB1	Eye / Retina
NPHP5-RD	NPHP5	Eye / Retina
Charcot Marie Tooth disease type 4J (CMT4J)	FIG4	Neurological
Multiple Sulfatase Deficiency	SUMF1	Neurological
Spastic Paraplegia, type 47 (SPG47)	AP4B1	Neurological
Spastic paraplegia 50 (SPG50)	AP4M1	Neurological
Barth Syndrome	TAZ	Cardiac
PGM1-Congentital Disorder of Glycosylation (CDG) (PGM1 deficiency)	PGM1	Inborn error of metabolism
Propionic Acidemia	PCCB	Inborn error of metabolism
Fibrodysplasia Ossificans Progressiva (FOP)	ACVR1	Orthopedic
Mucopolysaccharidosis IVA (MPS IVA, Morquio A Syndrome)	GALNS	Orthopedic

Table 1. Rare diseases and disorders received in the nomination process that were selected by the BGTC Steering Committee as candidates for further applications.

Background

The Foundation for the National Institutes of Health, a non-profit, 501(c)(3) charitable organization that supports the National Institutes of Health (NIH) in its mission to improve health by forming and facilitating public-private partnerships for biomedical research, is issuing a Request for Proposals (RFP) to support the Accelerating Medicines Partnership® (AMP®) Bespoke Gene Therapy Consortium (BGTC). The BGTC is executed by FNIH as a public-private partnership involving multiple NIH Institutes, Centers, and cross-Institute initiatives, the U.S. Food and Drug Administration (FDA), numerous pharmaceutical and biotech companies, non-profit organizations, and patient advocates. The BGTC is dedicated to making gene therapy a reality for people with rare genetic diseases affecting populations too small to be viable from the current commercial perspective. The goal of the BGTC is to evaluate methodologies to streamline the process of AAV gene therapy clinical trials initiation for pediatric and adult monogenic disease. Applicants can apply for the opportunity to advance an AAV gene therapy candidate through first-in-human clinical trials. The BGTC aims to select 5-6 diseases for the clinical program, and clinical trials will be supported by consortium partners who will produce the GMP vector to be used in IND-enabling studies and a human clinical trial. Given its precompetitive research focus, any publications and/or Intellectual Property (IP) generated from the efforts of the BGTC must adopt a "team science" approach and are intended to fall within the public domain, consistent with the AMP principles outlined herein.

Advancing access to AAV technologies and vectors for bespoke clinical applications has been focused on increasing the availability of AAV gene therapy approaches to populations of patients where no standard business case can be made for commercial therapeutic development. Manufacturing capacity limitations, efficiency of vector production, lack of adequate analytical/CMC assays, and human subject protection/regulatory issues pertaining to clinical studies have been identified as major roadblocks to broad and efficient use of AAV-based gene therapies for the thousands of very low prevalence human diseases whose molecular basis is understood and therefore have become candidates for bespoke gene therapy. The FDA has fully recognized the need for an end-to-end approach to the provision of individualized therapeutic products, particularly in the field of *in vivo* AAV gene therapy. The issues for these products include

determining the quantity of supportive preclinical evidence needed prior to patient treatment, understanding the clinical information that should be captured, and production of quality product fit-for-purpose – all in the context of an appropriate regulatory paradigm that facilitates safe patient treatment that has a reasonably high likelihood of being effective. Additionally, a sustainable way is needed to deliver these products if they show promise, since they are currently not considered viable from a commercial perspective. By creating the BGTC, the NIH, FDA and numerous private sector organizations have committed to working with a range of federal, industrial, academic, and advocacy organizations to address the unmet medical need in this area, including efforts to ensure that AAV gene therapies are available to all individuals who might benefit from them. See FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials | FDA.

As part of the consortium efforts, the BGTC will coordinate the manufacturing, Critical Quality Attribute (CQA) testing of manufactured product, pre-clinical testing in appropriate animal model(s), and delivery of AAV therapies to the selected clinical sites. The BGTC intends to use processes developed by the consortium to facilitate clinical trials for 5-6 of the rare genetic diseases and disorders in Table 1, which were selected from the nominations received and reviewed by the Steering Committee. Clinical trials for diseases other than those listed in Table 1 are outside the scope of this RFP.

BGTC manufacturer(s) will utilize their own process, standard operating procedures and prior manufacturing knowledge and expertise to produce the vector product, perform a subset of the required testing. Manufacturing services are not being solicited through this RFP. The NIH, through the National Center for Advancing Translational Sciences (NCATS), will establish a centralized testing facility to conduct product-specific supplemental testing (e.g., potency, standardized vector copy number, etc.) as needed. NIH will be the IND holder for all BGTC clinical trials and will provide a release certificate of analysis (CoA) in the IND. Final drug product labelling and CoA will be provided by NIH in the IND submission to FDA.

The BGTC will designate a Coordinating Center which will provide clinical trial oversight, data management and analysis, quality control, statistical considerations, and safety monitoring including management of the safety data and preparation of data for the Data Safety Monitoring Board(s) (DSMB) reports. More information about the anticipated role of the Coordinating Center can be found on page 8 of the BGTC concept document. Coordinating Center services are not being solicited through this RFP.

Award Information

I. Funds Available and Anticipated Number of Awards

The BGTC anticipates funding clinical trial proposals for 5-6 rare diseases and disorders from the candidate list in Table 1. The specific number of selections and the amount of support for each clinical trial award is contingent upon the submission of a sufficient number of meritorious applications and proper budget justification within the proposal. In no instance will multiple proposals be selected for the same disease or disorder.

II. Award Budget

Application budgets should reflect the actual scientific needs of the proposed project based on the study procedures and schedule. The BGTC anticipates funding 5-6 clinical trial awards at a total cost of approximately $10 - $17 Million. Indirect costs (F&A) must be 15% or less of direct costs. The final award amount will be negotiated between the parties The BGTC strongly encourages collaboration with an Investigator at the NIH and including the NIH Clinical Center as a trial site to help reduce costs.

III. California Institute for Regenerative Medicine (CIRM) Funding

BGTC and CIRM are partnering to coordinate their respective funding opportunities in order to maximize resources available for projects of mutual interest. During the application process, BGTC may recommend that California applicants or non-California applicants proposing research activities in California seek advice from CIRM and FNIH on appropriate funding opportunities to support their projects' participation in the consortium. Information on CIRM's Funding Opportunities may be found at this link: https://www.cirm.ca.gov/researchers/funding-opportunities

For more information contact CIRM at Clinical@cirm.ca.gov

IV. Award Project Period

The BGTC clinical program will consist of a planning phase and an execution phase. The planning phase will consist of coordinating center standup, the IND submission, vector manufacturing, QC testing, IND-enabling pre-clinical studies, patient identification, clinical protocol development, and IRB approvals, which is expected to occur from 2023-2024, shortly after the final disease selection. During the planning phase, the investigator will participate and advise on technical matters in a consultative capacity. BGTC expects the clinical trials execution phase to begin in or around 2025. Considerations for the timing of primary and follow-up components of the clinical study are described below.

Primary Study and Follow-ups

The design of the proposed clinical trial should determine the award project period. The general expectation is to perform primary outcome assessments within 1-2 years. Primary study follow-up of treated participants may extend beyond this timepoint as warranted for the indication and FDA requirements, but primary study follow-up should not exceed a total project period of 5 years.

Long-term follow-up

The active period of BGTC support is currently planned through Q4 2026. Notwithstanding any possible extensions, follow-up beyond this active period of support is encouraged and should be considered as part of the clinical & regulatory plan, but alternative funding sources would be required. Applicants should review relevant health authority guidance (e.g. FDA) for gene therapies when determining long-term follow-up duration and assessments for treated study participants. Applicants may consider utilizing existing patient registries for long-term follow-up, provided criteria for assessments are met and appropriate oversight of data can be ensured by the sponsor. A specific example is the current hemophilia gene therapy registry studies being conducted by non-profit groups. The applicant's institution accepts responsibility for ensuring appropriate follow-up of gene transfer participants in accordance with FDA and other relevant health authorities' recommendations and acknowledges that this responsibility extends beyond the period of active BGTC support.

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V. Study Location

The study will be conducted in the US and must comply with all applicable US regulations. However, BGTC recognizes the potential challenges associated with recruiting patients for rare disease studies and is willing to consider the inclusion of international patients. Where challenges with patient enrollment in the US is expected, proposals may discuss the option of travel for

international patients to the US or the inclusion of an international site. However, cost will be a factor in the final determination of awards.

VI. Roles and Responsibilities

The Roles and Responsibilities for major tasks are described in the table below (applicant responsibilities under this RFP which must be addressed in the proposal are in **bold**):

Activity	Responsible Party
Vector manufacturing	BGTC / CMO
Vector analytical testing	BGTC / CMO
Product packaging, distribution	BGTC / CMO
Pre-Clinical study design	BGTC / CMO with **Applicant input** (see study protocol)
Pre-Clinical study execution	BGTC / CMO
CMO oversight	NIH / FNIH
Clinical study design	**Applicant**
Clinical study sponsor / IND holder	NIH
Clinical study execution (years 1-5)	**Applicant**
Patient follow-up after year 5 (optional)	**Applicant**
Medical safety monitoring	NIH Coordinating Center, in consultation with Applicant
Data entry/Study Coordinator/Study Nurse	**Applicant**
Clinical Trial insurance	**Applicant**
Central IRB	NIH Coordinating Center
Data Safety Monitoring Board	NIH Coordinating Center
Data analyses for DSMB meetings	NIH Coordinating Center
Data Management and Analysis	NIH Coordinating Center
Study Personnel Training and Certifications	NIH Coordinating Center in consultation with Applicant
Design and Implementation of a Quality Assurance Program	NIH Coordinating Center
Develop Standard Operating Procedures (SOPs) addressing all aspects of data management and statistical analysis	NIH Coordinating Center
Transfer data to statistician and others for interim analysis as needed, and at the end of follow-up, cleaning and closing-out the database and submit study results for data sharing.	NIH Coordinating Center
Tracking of Regulatory documents	NIH Coordinating Center
Clinicaltrials.gov submission, updates and reporting of study result	**Applicant**
Publication and Presentation of Clinical Trial Results	Applicant + BGTC representatives

Eligibility Information

Organizations eligible to apply are:

- Private or public medical/scientific research institutions, including NIH intramural program
- US-based or international organizations (international organizations must comply with all US FDA requirements)
- Able to comply with the necessary AMP BGTC IP, data sharing, and publication guidelines as outlined in Section II.

Program Overview Participation

Successful applicants will become participants in the BGTC, not just funding recipients, and are expected to adhere to AMP principles. The BGTC has adopted a "team science" approach, which emphasizes collaboration and data sharing. Specific considerations for Intellectual Property and publications are outlined in Section II below. More information is found in the BGTC concept document.

Application and Submission Instructions

I. Submission Deliverables

Complete applications will include:

- BGTC Clinical Trials Proposal Submission Form (Appendix 1, Page 1)
- **Phase 1/2 IND Clinical Trial Protocol Template, Appendix 2.**

*****COMPLETE SECTIONS 1 – 5, 6.1, 6.5, 8.1, 8.2, 8.3.8, AND 9.2 ONLY*****
(Sections that are greyed out do not need to be addressed)

- Attachments
  - Budget worksheet (Appendix 3) (expected to be released in August 2022)
  - Informed Consent form, patterned after Appendix 4, Informed Consent Template
  - Biosketches of Key Personnel
  - Race and Ethnicity Diversity Plan (see Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry; Availability | FDA).
  - Clinical trial insurance policy / certificate

II. Data, Publications and Intellectual Property

All applicants will be expected to comply with the AMP BGTC Principles as outlined below.

Data and Publications
This project will operate under a "team science" approach, and all publications and data resources generated by recipients of BGTC funding must acknowledge BGTC investigators and/or funder(s) and be made publicly accessible within 6 months of publication. Specific publication strategies will be discussed with the BGTC Steering Committee as needed. Publications generated by the Steering Committee will have joint authorship. Specific publication strategies will be developed by the Steering Committee prior to project start, including proposal for lead authors and co-authors.

Intellectual property (IP)
Given its precompetitive research focus and commitment to making results of that research available as broadly and promptly as possible, it is not expected that BGTC will generate novel IP. BGTC award recipients may use pre-existing IP for work done under the partnership. BGTC research

awardees agree not to file patent applications on research discoveries made under the partnership, except in the rare instance when a consensus of FNIH and the BGTC agree that it is in the best interests of the partnership and public health to do so. IP developed by the NIH or under NIH awards are subject to applicable Federal law, regulation, and policies.

III. Page Limits

- Please limit the main body of your proposal, addressing Appendix 2, Phase 1/2 IND Clinical Trial Protocol Template, Section 1 – 5, 6.1, 6.5, 8.1, 8.2, 8.3.8, and 9.2 only, to no more than 25 pages in length (single spaced, 11-point Arial or Times New Roman font, 1-inch page margins), including figures and legends.
- The Budget Worksheet (Appendix 3) should not exceed 2 pages.
- Biosketches for Key Personnel should not exceed 3 pages each.
- Additional information may be included as an attachment, with no specified limit. The Disease Selection Working Group reserves the right to limit review of material in the attachment as needed.

IV. Award Reporting

For those applications selected for funding, the Principal Investigators on the application should expect to submit progress updates for the project at a frequency and in a format to be determined by the BGTC Steering Committee, but no less frequently than annually.

V. Additional Information Required

Please provide any existing IP or patent information relevant to the assay that may affect its use in the partnership, or the banking of any resulting data funded by this effort in a public controlled access database for use after initial publication of the findings. Further guidance is available upon request.

VI. Submission Instructions

Send responses via e-mail to BGTC@fnih.org with a copy to Mr. Brad Garrison, Senior Project Manager (bgarrison@fnih.org). Alternatively, applicants may submit larger-sized files via the NIH Secure File Transfer Service: https://secureemail.nih.gov/bds/Login.do, with a corresponding email notice to BGTC@fnih.org and bgarrison@fnih.org.

VII. Evaluation factors for award

A. GENERAL

Selection of an offeror for contract award will be based on an evaluation of proposals against three factors. The factors in order of importance are: technical, cost, and past performance/qualifications. Although technical factors are of paramount consideration in the award of the contract, past performance, and cost/price are also important to the overall contract award decision. All evaluation factors other than cost or price, when combined, are significantly more important than cost. The BGTC intends to make award(s) to the offeror(s) whose proposal(s) provide the best overall value to the Consortium.

The evaluation will be based on the demonstrated capabilities of the prospective Contractors in relation to the needs of the project as set forth in this solicitation. The merits of each proposal will be evaluated carefully. Each proposal must document the feasibility of successful implementation

of the requirements of the RFP. Offerors must submit information sufficient to evaluate their proposals based on the detailed factors listed below.

B. PRE-AWARD SITE VISIT OR SITE AUDIT

Following completion of the scientific/technical peer review and after determination of the Competitive Range, Offerors may be subject to a pre-award reverse site visit/webinar. The decision to conduct a pre-award site visit after review will be made by the BGTC Steering Committee or designee. Offerors, including proposed subcontractors, will be requested to make all non-proprietary records, including previous regulatory inspection records, and staff available in response to a pre-award reverse site visit by the BGTC or its designee. Due to timeline requirements, pre-award reverse site visits may be made with short notice.

C. TECHNICAL EVALUATION CRITERIA

The evaluation criteria will be used by the technical evaluation committee when reviewing the technical proposals. The criteria are listed below in the order of relative importance with weights assigned for evaluation purposes. Sub-factors are listed in order of relative importance.

TECHNICAL EVALUATION

CRITERION 1: TECHNICAL PLAN/APPROACH

Appropriateness, feasibility, and adequacy of the proposed technical plan/approach for accomplishing the tasks outlined in the proposal and the overall objectives of the BGTC including capacity and capability for a broad range of services necessary to support and conduct clinical trials and bioanalysis and when needed, conduct domestic or international natural history, or observational studies. Adequacy of proposed plan to address relevant biological variables, including sex for studies in human subjects as applicable.

CRITERIA WEIGHT…… 100

CRITERION 2: SCIENTIFIC AND TECHNICAL PERSONNEL

Appropriateness and adequacy of the education, training, experience, expertise, and proposed levels of effort of the Principal Investigator and scientific and technical staff including subcontractors/consultants for accomplishing the tasks outlined in the proposal and the overall objectives of the BGTC clinical trials component.

CRITERIA WEIGHT……...……40

CRITERION 3: PROJECT MANAGEMENT

Appropriateness and adequacy of the plans for Project Management in terms of staffing, organizational structure and lines of authority, management of subcontracts/consultants, tracking of project activities, monitoring progress and timelines, and communication with stakeholders.

CRITERIA WEIGHT……..……..……40

CRITERION 4: FACILITIES, EQUIPMENT, AND OTHER RESOURCES

Appropriateness and adequacy of facilities, equipment, space and other resources including those of

subcontractors/consultants for accomplishing the tasks outlined in the Statement of Work and the overall objectives of the solicitation.

CRITERIA WEIGHT……..……20

TOTAL POSSIBLE 200

OTHER EVALUATION FACTORS:

A. HUMAN SUBJECT EVALUATION

   Protection of Human Subjects from Research Risks, Data and Safety Monitoring

B. RACE AND ETHNICITY DIVERSITY PLAN
C. EVALUATION OF DATA SHARING PLAN
D. COST FACTOR
E. PAST PERFORMANCE/EXPERIENCE FACTOR

Key Dates

Informational webinar: August 30, 2022, 11:30 AM – 1:00 PM ET

Application Due Date: October 31, 2022, 11:59 PM ET

Targeted Application Review Period: November 1, 2022 – January 31, 2022
The AMP BGTC Clinical Subteam and Disease Selection Working Group reserve the right to contact the applicant(s), through the FNIH Project Management team, if additional information is needed from the applicant(s).

Potential Oral Presentations from Finalists (*If Needed*):
Applicants will be informed after initial review of proposals whether they will need to provide an oral presentation with the ability for Q&A to the AMP BGTC Steering Committee or Clinical Subteam.

Expected Award Announcement: February 2023*
Applicants will be notified by email of the outcome of the RFP.

**FNIH reserves the right to modify the target deadline*

Expected Award Start Date: April 2023

About the Foundation for the NIH

Established by the United States Congress to support the mission of the NIH – improving health through scientific discovery in the search for cure – the Foundation for the NIH is a leader in identifying and addressing complex scientific and health issues. The Foundation is a non-profit, 501(c) (3) charitable organization that raises private-sector funds for and manages a broad portfolio of unique programs that complement and enhance NIH priorities and activities. For additional information about the Foundation for the NIH, visit www.fnih.org.

Appendix 1

BGTC Clinical Trial Proposal Submission Form

Title of Project		
Principal Investigator(s) (submitter) Name: Title: Submitting Organization: Address: e-mail: Tel: ***Co-investigator(s) (add more as needed)*** Name: Title: Submitting Organization: Address: e-mail: Tel:		
Disease or Disorder:		
Submission Date:		
Time Period of Project:		
Project Total Budget:		
Internal Use Only		
WG Decision, Date:		
Steering Committee Decision, Date: *(if needed)*		
Executive Committee Decision, Date: *(if needed)*		