REQUEST FOR COLLABORATION

CENTRAL GENETICS LABORATORY

FOR

THE GRADE STUDY

Glycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness Study

COLLABORATING CENTRAL GENETICS LABORATORY

Date: 5/18/2018

https://grade.bsc.gwu.edu/web/grade/gradeCGL

Letter of Intent Due: July 10, 2018
Proposal Due: August 15, 2018

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CENTRAL GENETICS LABORATORY
REQUEST FOR COLLABORATION (RFC)

1. INTRODUCTION

The George Washington University, on behalf of the **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness (**GRADE)** Study Research Group, is seeking a leading geneticist(s) and collaborating organization to serve in the role of the ***Central Genetics Laboratory (CGL)***. This Request for Collaboration (RFC) seeks applications to serve in this role. Through a peer review selection process, a collaborating genetics laboratory will be selected along with its lead geneticist who will serve as the Director of the GRADE CGL. *This solicitation will NOT involve provision of funding.* Rather, the selected genetics laboratory and its principal investigator, will collaborate with the GRADE Principal Investigators (PIs) David Nathan and John Lachin, and other GRADE investigators, to then prepare a grant application (e.g., R01) to be submitted to the NIH (or other agencies) to request funding to conduct the ***GRADE Genomics Sub-study*** activities of the CGL. The grant application will be submitted by The Biostatistics Center of the George Washington University that serves as the Coordinating Center for GRADE with Dr. Lachin as the Contact PI. The selected geneticist will be the PI of the CGL as part of the GRADE consortium. If the grant is awarded, GWU will be the prime awardee and will provide funding to the CGL through a sub-agreement from the George Washington University to the CGL's institution. It is possible that the study may be funded as early as October, 2019.

The purpose of this announcement is to seek applicants with the interest, scientific expertise, experience, facilities and resources necessary to function as a Central Genetics Laboratory in the GRADE Study. For further details see **Section 5, Technical Evaluation Criteria.**

2. GRADE SUMMARY

The epidemic of type 2 diabetes that has affected the US and other populations in the last half of the 20th and first part of the 21st centuries threatens to become the major public health problem of this century, affecting up to 1 in 3 Americans if current trends continue. The most recent estimates in the US include a prevalence of more than 24.5 million persons with type 2 diabetes, with an incidence of 1.9 million new cases per year. The major human and economic costs associated with the epidemic are related primarily to the development of long-term complications including retinopathy, nephropathy, and neuropathy that cause more cases of blindness, renal failure, and amputations than any other disease. Cardiovascular disease is increased 2-5 fold in type 2 diabetes and is the leading cause of premature death. High quality clinical trials have established the importance of lowering glycemia with a variety of medications to reduce the long-term complications. One of the major challenges for practitioners is to choose, from the considerable armamentarium of glucose-lowering medications at their disposal, the optimal approach to achieving and then maintaining good glycemic control for as long as possible. Evidence supporting the choice of one versus another agent as initial therapy or as the second drug added to metformin, the consensus initial treatment for type 2 diabetes, is lacking. Comparative effectiveness research is a high priority both to improve public health and to maximize cost-effectiveness in the management of type 2 diabetes. Moreover, efforts to individualize therapies and determine whether some therapies work better in individuals with particular characteristics compared to others are needed, and the differential effects of various therapies on the physiology of glucose metabolism also remain unknown.

The **G**lycemia **R**eduction **A**pproaches in **D**iabetes: A Comparative **E**ffectiveness (GRADE) Study is addressing these questions in a randomized clinical trial in patients with <10 years duration of diagnosed type 2 diabetes that will compare the metabolic effects of four common glucose-lowering drugs when combined with metformin. The four randomly assigned medications are the sulfonylurea glimepiride, the DPP-4 inhibitor sitagliptin, the GLP-1 agonist liraglutide, and the basal insulin glargine. A total of 5047 participants who are within 10 years of diagnosis and are being treated with metformin at the time of recruitment have been enrolled. These subjects have been randomly assigned to one of the four agents, which was added to metformin, to compare the effects among these four combinations. The proposed study is being performed over a clinically meaningful duration, with a possible mean follow-up of over 5 years, not accounting for losses to follow-up.

The *primary metabolic outcome* will be the time to primary failure defined as a hemoglobin A1c (HbA1c) ≥7%, subsequently confirmed, after having been treated with maximally tolerated doses of both metformin (up to 2,000 mg per day) and the randomly assigned second medication (intention-to-treat). A *secondary metabolic outcome* will be the time to an HbA1c >7.5%, confirmed. At that time, basal insulin "rescue" therapy will be added for the subjects assigned to drugs other than insulin, and insulin therapy will be intensified for those assigned to basal insulin. Another metabolic outcome is the time to tertiary metabolic failure defined as the time to another HbA1c >7.5%, confirmed, after treatment with basal insulin, at which time more intensive insulin therapy is initiated. Other metabolic outcomes to be studied include the mean HbA1c and measures of insulin secretion and sensitivity over the entire study duration and at intermediate time points. Other important attributes of the four drug combinations to be assessed include adverse effects such as weight gain and hypoglycemia, effects on cardiovascular disease (CVD) risk factors, tolerability and quality-of-life, and cost and cost-effectiveness. Although the GRADE study is not primarily a clinical outcomes study, selected measures of microvascular disease will be included as secondary outcomes and clinical cardiovascular outcome events will be recorded. We will also examine the phenotypic characteristics that are associated with metabolic response to and/or failure of the individual medication combinations. Mechanistic studies of the pathophysiology contributing to success or failure of individual combinations will be part of the trial. The sub-study that forms the basis of this RFC would aim to identify the genetic determinants of drug response.

When basal insulin (glargine) is added to metformin and the assigned medication at the time of secondary metabolic failure in participants who were originally assigned to medications other than insulin, the same insulin adjustment protocol as implemented for the participants originally assigned to glargine will be used. If tertiary metabolic failure then occurs, metformin and basal (glargine insulin) will be continued, the originally assigned medication will be discontinued, and the insulin regimen will be intensified with the addition of rapid-acting insulin according to the study insulin protocol.

Similarly, if the participants originally assigned to basal insulin reach the secondary metabolic outcome following the primary outcome, their metformin and basal insulin will be continued and the insulin regimen will be intensified. The systematic, study-wide implementation of intensified ("rescue") insulin therapy will allow the study to determine the relative effectiveness of the four assigned therapies to affect the time period until intensified insulin therapy (basal insulin plus rapid-acting insulin) is necessary.

The major specific aims of this clinical trial in metformin-treated patients with <10 years duration of diagnosed type 2 diabetes include:

- Comparison of the relative effectiveness of four commonly used glucose-lowering medications with different glucose-lowering mechanisms, when used in combination with metformin, in maintaining metabolic control, defined as time-to-primary failure with an HbA1c

≥7.0%, confirmed, while on maximally tolerated doses of both metformin, up to 2,000 mg per day, and the assigned medications;

- Comparison of the relative attributes, including the durability of the glucose-lowering effects and other metabolic outcomes, adverse effects, effects on CVD risk factors and quality-of-life, tolerability and cost-effectiveness, of the four glucose-lowering medications used in combination with metformin;
- Comparison of the cumulative incidence of diabetic complications, such as microalbuminuria, among the randomly assigned agents;
- Determination of the phenotypic characteristics associated with response to and failure of the four different medication combinations;
- Evaluation of factors that determine the success and/or failure of specific regimens over time, including mechanistic studies of beta-cell failure/preservation over time;
- Determination of the relative effects of the four combinations on the time to secondary metabolic failure, with an HbA1c >7.5%, confirmed, requiring the need for rescue therapy;
- Determination of the relative effects of the four combinations on the time to the need to implement intensive insulin therapy with basal plus rapid-acting insulin.

The results of this trial will identify the most effective means of treating type 2 diabetes and will have major public health implications.

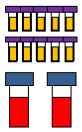
Recruitment was completed in 2017 with 5047 participants randomly assigned to one of the four GRADE interventions. As noted below, DNA samples and stored packed cells are available on the large majority of participants at baseline, prior to starting study medications. The cohort has been intensively phenotyped (see table 2 in protocol (appendix)) that describes measurements in GRADE) and samples for microbiome analyses have been collected.

3. DESCRIPTION OF SAVED SPECIMENS FOR GENETIC STUDIES

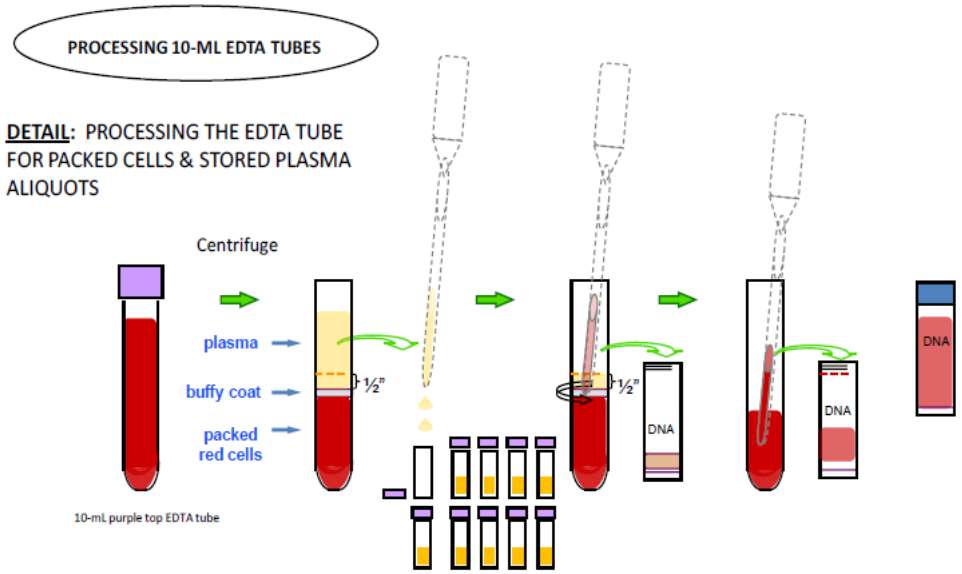
At the Baseline visit, blood was collected in two 10 mL EDTA-anticoagulated blood collection tubes from all consented participants. These blood tubes were centrifuged for removal of the plasma supernatant. The buffy coat and packed cells from each blood collection tube were transferred to 2 vials (approximately 5 mL each) and frozen prior to shipment to the Central Biochemistry Laboratory (CBL). A summary of this process is shown in the table and processing diagram (see diagrams below). At the CBL, one of the vials was used for DNA extraction. DNA was extracted using either Puregene reagents on the Qiagen Autopure instrument or Qiagen Flexigene reagents on the Autogen FlexSTAR Plus Automated extraction platform. The DNA extract is stored in stock (non-normalized) and diluted (normalized to 200 ng/uL) concentrations at -70^{o}C. If the stock vial DNA quantity was less than 100 ug, DNA was extracted from the second vial of packed cells; the extract from the 2nd packed cell vial is also stored in stock and diluted concentrations. For the remainder of the participants, one packed cell vial remains stored at -70^{o}C.

In rare instances (for example, because of a change in consent), the two 10 mL EDTA-anticoagulated blood collection tubes used for DNA extraction may have been collected at a visit other than the Baseline visit. Blood samples on participants for whom both vials of packed cells yielded insufficient DNA quantity may also have been recollected at visits other than the Baseline visit.

See the following diagrams:

Glucose, insulin, c-peptide DNA Plasma Storage	Tube #3	Fasting	10 mL purple-top EDTA	Label tube 	Label vials 	• Fill **labeled** tubes completely with blood • Invert tubes 8 times • Place tube into ice bath immediately • Centrifuge tubes at 2,000 x g for 15 min • Aliquot 0.5 mL plasma into **10** labeled 2-mL cryovials. Tightly fasten with purple screw caps • Aliquot packed cells into **2 labeled** 5-mL transport vials and fasten with blue caps (see detailed instructions) • Freeze upright at -70°C until shipment preparation
DNA Plasma Storage	Tube #4	Fasting	10 mL purple-top EDTA	Label tube 		

Appendix D. Collection and Processing Flow Diagrams
GRADE Baseline Lab Visit



1. Centrifuge the 10-mL EDTA tubes at 2,000 x G for 15 minutes.
2. Taking care not to disturb the cell layer, remove the clear plasma supernatant and transfer 0.5 mL plasma into each of 10 labeled 2-mL cryovials. Aspirate slowly starting at the top of the plasma. Leave a ½ inch layer of plasma above the buffy coat-red blood cell layers. It is important to withdraw only the plasma and none of the buffy coat (containing white blood cells and platelets) that forms at the cell-plasma interface following centrifugation. If some of the buffy coat is accidentally aspirated while removing the plasma, re-centrifuge the tube under the initial processing conditions. Fasten purple screw caps tightly onto the cryovials.
3. Using the same plastic transfer pipet, slowly aspirate the remaining ½" layer of plasma, the buffy coat and *some* of the remaining red cells from the tube. Take care not to aspirate the buffy coat into the bulb of the pipet! 'Ring' the tube with the pipet by carefully aspirating along the wall at the buffy coat layer to ensure maximum transfer. Dispense into the 5-mL 'DNA' vial.
4. Still using the same plastic pipet, transfer all of the remaining packed red cells from the tube into the same 5-mL'DNA' vial. This step will ensure that all of the buffy coat is adequately rinsed from the pipet. Repeat with the second EDTA tube. Fasten blue screw caps tightly on the vials.

4. DESCRIPTION OF WORK

The Central Genetics Laboratory (CGL) will be a collaborator with the GRADE Study Research Group. The purpose of this solicitation is to select a senior geneticist to collaborate with the GRADE investigators to design and plan genetic studies to be added to GRADE. The immediate task will be for the geneticist collaborator(s) and GRADE to prepare a grant application to be submitted to seek funding for the GRADE genetic studies. The target date for submission is February, 2019. Thus, we are requesting that applicants to serve as the GRADE genetics collaborator should address the work tasks to be performed after a successful grant application has been funded.

For purposes of this application, it should be assumed that genomic material will be available for at least 95% of the 5047 participants enrolled into the study.

Under the GRADE genetics sub-study, the GRADE Central Genetics Laboratory (CGL) will be responsible for the following, which should be included in the CGL budget and proposal:

1) The PI of the CGL will also be the Scientific Principal Investigator of the GRADE Genomics Sub-Study.
2) The application should include a specific proposal for the aims and objectives of the GRADE Genomic Sub-Study, with specific hypotheses and scientific rationale, and the specific genomic assessments proposed to meet those objectives.
3) Although the Study Group considers pharmacogenomics to be the area that GRADE is best suited to address, applicants should feel free to propose any genomic studies, and accompanying methods, that they consider of scientific and clinical importance and that GRADE can address.
4) For each proposed assay the application should describe the methods to be employed and the quality assurance processes to be applied.
5) The **Timeline** and work for the sub-study are as follows, assuming a start date of October 1, 2019:
   Months 1-3 (startup): Obtain local IRB approval for the GRADE Genomics Sub-study. Establish procedures for sample transition from the Central Biochemistry Laboratory to the CGL, sample accession into the CGL, data reporting to the Coordinating Center, and ultimately the final storage of specimens with the NIDDK Genetics Repository.
   Months 4-27: Conduct genomic assays and report results to the Coordinating Center. Quality assurance reports are assessed periodically by the GRADE Quality Assurance Working Group.
   Months 28-36: In collaboration with GRADE investigators and statisticians, develop and perform a full analysis plan for the primary objectives of the GRADE Genomics Sub-Study.
   Final 9 months of the study: Participate in the development of additional (ancillary) analysis plans and the writing of presentations and publications, and archival of the biological specimens with the NIDDK genetics repository. Note that statistical support for data analyses will be provided by the Coordinating Center statisticians.
6) Provide the following electronic data transmissions and reports to the Coordinating Center:

	Type of Data/Report	**Frequency**
1.	Specimen and Assay Results Reports	In a timely fashion
2.	Specimen Problems Reports	In a timely fashion
3.	Discrepancies Report between samples reported and results transmitted	In a timely fashion
4.	QC Reports of quality control surveillance	Periodically, as requested
5.	Throughput Reports of specimen processing and assay results reporting to the Coordinating Center	Bi-Monthly
6.	Other reports as requested	TBD

7) Collaborate with the GRADE Study Research Group to investigate the reasons and propose solutions for any problems with shipment of samples, performance of assays, or reporting of results.
8) Resolve and report discrepancies between samples reported and results transmitted on a timely basis.
9) Collaboratively with the GRADE Study Research Group, establish the throughput time for results of genetic testing and sequencing to be transferred to the Coordinating Center at the CGL to meet the needs of the study. All genomic data should be transferred to the Coordinating Center in a timely manner as they are accrued.

10) All genomic assays should be completed and the data transferred to the Coordinating Center by the close of Month 27 of the award.
11) Identify procedures for the internal bench quality control of all testing (e.g., genotyping and/or sequencing) conducted by the laboratory.
12) Host site visits by the Coordinating Center and study representatives during the study on an *ad hoc* basis.
13) Participate with other GRADE investigators to develop plans for the presentation and publication of results of the GRADE Genomics Sub-study. This includes specification of the topics to be addressed in each paper, developing an analysis plan for each paper and participating as a co-author of each paper. The detailed statistical analyses will be conducted in collaboration with the statisticians at the GRADE Coordinating Center.
14) Provide long-term storage of samples/specimens or genetic material as directed by the Steering Committee. The CGL will not dispose of any samples/specimens or genetic material without written authorization of the Steering Committee and will provide annual inventories for stored samples and as requested.
15) At the end of the study, the CGL will provide the NIDDK DNA Sample Repository with stored aliquots of specimens collected from GRADE participants. Samples will be identified in accordance with NIDDK repository guidelines.
16) The CGL will also archive the genomic data with the NIDDK Data Repository in accordance with NIDDK genomic data sharing policies.
17) Prepare and conduct study closeout activities.

The CGL PI will represent the laboratory at appropriate GRADE committee meetings, including but not restricted to Steering Committee meetings, and provide scientific input related to genotyping and/or sequencing methodology, conduct, and analysis for the study. The Laboratory PI or similar qualified staff is expected to attend annual GRADE Study Research Group meetings, as required. The Laboratory PI will participate in appropriate committee meeting or conference calls.

5. PROPOSAL INSTRUCTIONS

5.1. GENERAL INSTRUCTIONS

It is anticipated that an eminent geneticist and an established research center will be selected through this solicitation to serve as the PI of the GRADE CGL. The CGL, jointly with GRADE investigators, will then submit an application for funding to conduct the GRADE Genomics Sub-Study. The CGL component of this sub-study would be funded through an incrementally funded cost-reimbursement subagreement awarded by the George Washington University that is the prime GRADE award recipient.

The instructions below establish the minimum acceptable requirements for the format and content of the proposal. The George Washington University reserves the right to reject any and all proposals not meeting the following minimum acceptable requirements for the format and content of the proposal.

While the present Request for Collaboration (RFC) will not lead to any funding, in order to select the best collaborator from the perspective of scientific merit and fiscal value, we are asking that all applicants to this RFC prepare a budget to complete the above workscope. The objective is to select a CGL collaborator with whom we could submit an application for funding in February of 2019. Thus, we request that the budget be prepared with funding starting October, 2019 as Month 1 under the timeline stated above.

The proposal shall be signed by an individual authorized to bind the applicant organization. **Proposals shall be submitted in a single PDF file electronically to the following email address: GRADE.LabApplications@bsc.gwu.edu.** Proposals should be prepared using no smaller than Arial 11 point font, with 1” margins. **Email all questions to: GRADE.LabApplications@bsc.gwu.edu**

DEADLINE: Proposals must be received by The George Washington University Biostatistics Center at the email address above by close of business (5:00 PM Eastern) Wednesday August 15, 2018.

Questions regarding proposal should be directed to:

For Technical Questions:
John M. Lachin, ScD
PI, GRADE Coordinating Center
Tel: 301-816-8081
jml@bsc.gwu.edu

For Fiscal and Budget Questions:
Grace Nogan, MBA
Assistant Director of Administration
Tel: 301-881-9260
gnogan@bsc.gwu.edu

5.2. LETTER OF INTENT

It is requested that organizations intending to submit a proposal in response to this Announcement inform The George Washington University Biostatistics Center of their intent by writing a letter providing the organization name, Principal Investigator, address, phone and email. Letters should be emailed to **GRADE.LabApplications@bsc.gwu.edu** and should be received by **Friday, July 10, 2018.** A Letter of Intent (LOI) is requested to assist in the review process but is not required in order to submit an application. Institutional signature not required on LOI.

Letters of Intent should be addressed to:

John Lachin, Sc.D.
The George Washington University, Biostatistics Center
6110 Executive Blvd, Suite 750
Rockville, MD 20852.

5.3. INSTRUCTIONS FOR ORGANIZATION AND CONTENT OF TECHNICAL PORTION OF PROPOSAL

The organization and content of the technical portion of the proposal should be as follows:

5.3.1 Cover Letter

A cover letter should be included and signed by a person authorized to commit the applicant organization to performance of the project.

5.3.2 Table of Contents

Indicate the page locations for each of the principal sections of the proposal and additional detail as appropriate.

5.3.3 Executive Summary

Include a brief summary outlining the applicant organization's goals, methods, facilities, and other material to aid reviewers by providing a perspective for evaluation of the detailed proposal. This should not exceed 30 lines.

5.3.4 Technical Application

Describe present knowledge and state of the art in the conduct of the individual assays required for this sub-study and in the role of serving as a central genomics laboratory for a multicenter clinical trial or consortium. Provide information on current laboratory certification(s) if applicable.

5.3.5 Research Plan

Provide the technical approach to be taken in meeting the objectives of the CGL and in performing the work described in Section 4. **The research plan should not exceed 12 pages.** The research plan should include but not necessarily be restricted to the following:

a) Statement of procedures for specimen handling, labeling, and shipping from the GRADE Central Biochemistry Laboratory to the CGL proposed for implementation in the trial. The statement of procedures should be in detail sufficient to form the basis for a section of the GRADE Manual of Laboratory Procedures for the CGL.

b) A discussion of the preferred approach for genetic testing (i.e., genotyping, sequencing, type of array or platform, exomes, genomes), with budget considerations and potential alternatives.
c) For each of the tests for genetic analyses (e.g., genotyping or sequencing) proposed, the specific method should be described with supporting data to document the precision and accuracy of the proposed methodology, including validation.
d) A description of the procedures for internal quality assurance/quality control surveillance to be employed by the central laboratory to monitor the bench performance of all assays, both for samples and for genetic variants.
e) Sample or template reports per list in the Scope of Work should be provided with the application.
f) The procedures for cataloging and long-term storage of specimens received; in addition, procedures to be employed for the retrieval of selected specimens for additional assays.
g) The procedure for timely communication of results to the coordinating center.
h) The suggested analytical approach, including method of association between genotype and phenotype, relevant covariates, controls for confounding, missing data, and thresholds for statistical significance.
i) Appropriate power calculations.
j) Available venues for replication/validation/extension of genetic findings.
k) Timeline.

5.3.6 Qualifications

The experience, qualifications, competence, availability, and level of effort of the applicant's team should be clearly defined in terms of the responsibilities of the CGL including biochemical assays to be conducted and in terms of serving as a collaborating facility for a multicenter collaborative investigation.

The statement of qualification should not exceed 3 pages.

a) Personnel

Provide information on the composition of personnel assigned to this project, their general qualifications, and recent experience with similar projects. Special mention should be made of direct technical supervisors and key technical personnel, and the approximate percent effort or amount of their total time each will devote to this project.

- Principal Investigator
  List the name of Principal Investigator (PI) who will serve as the key contact for technical aspects of the project. Describe the qualifications, experience, and accomplishments of the Principal Investigator including a description of the PI with respect to participation in collaborative multi-center clinical trials or other large studies, service on committees, collaborative efforts and co-authorship of study publications. State the estimated percent effort or amount of time to be spent on the project and the areas for which he/she will be responsible.
- Other Investigators
  List all other investigators who will be participating in the project. Discuss the qualifications, experience, and accomplishments. State the estimated time each will spend on the project and the areas or phases for which each will be responsible.
- Additional Personnel
  List names and titles of additional personnel, if any, and their role on the project and their relevant qualifications and experience

b) Institutional Experience

Provide information on recent experience with similar research studies making special notation of similar or related projects provided to the government or other sponsors if not conducted by the proposed research team. Include documentation which references the applicable contract or grant numbers and supervising cognizant agencies, giving names and telephone numbers of the Contract or Grants Officer and Project Officer. Provide

information on previous experience or working relationships with the proposed subrecipient and your applicant organization's experience in managing subagreements.

5.3.7 Facilities and Equipment

The applicant should describe existing facilities and equipment available for conducting the proposed project and justify in terms of research needs any new facilities or equipment to be acquired. Provide information on current laboratory certifications.

Facilities and equipment should not exceed 2 pages.

5.3.8 Organization and Administration

This section should not exceed 1 page.

a) Describe the administrative relationships of the proposed project within the organization including:
   - which department or office within the organization will have administrative responsibility for the project;
   - how the study will relate to other departments or research groups in the organization and specifically what organizational or other means will be used to encourage participation of scientists with relevant interest in the research of the project;
   - who would be responsible for the appointment of a new Project Director, should the incumbent leave.

b) Describe the organization of the project including the names of personnel who have been selected.

c) Show chain of responsibility in the project for:
   - administrative matters
   - planning and conduct of the project

5.3.9 Biosketches

Biosketches are required for the Principal Investigator, other investigators, and any additional key personnel including consultants. Indicate educational background, recent experience, publications and specific or technical accomplishments. Please use standard NIH format.

5.3.9 Dualities of Interest

All collaborating investigators named in the application, including those who may not receive salary, should complete a GRADE Duality of Interest Form in accordance with the GRADE Duality of Interest Policy statement. The policy and form are provided on the GRADE website for this Request for Collaboration.

5.4. Instructions for Organization and Content of the Budget Portion of the Proposal

The George Washington University Biostatistics Center serves as the Coordinating Center for the GRADE study

For the purposes of this solicitation, we are requesting that CGL applicants use the standard PHS398 forms. Only the PHS398 forms listed below are required. Instructions for completion of these forms can be found at: http://grants.nih.gov/grants/funding/phs398/phs398.html. However, please note that for the full cooperative agreement application to be submitted in late 2018, we will request that the selected applicant utilize the SF424 with all appropriate documentation. The official and full proposal from GWU to NIH/NIDDK will be submitted using the Grants.gov electronic submission process.

5.4.1 Organization and Content of Budget Section of Proposal

Following the technical portion of the proposal, applicants should submit a budget to perform the above described workscope in the **3-year time frame starting October 1, 2019**. Note that salaries paid on NIH funded projects cannot exceed the NIH salary cap.

1. Project funding will start October 1, 2019 and the fiscal year will end September 30th of each year. During the first three months the laboratory should prepare for study launch,

prepare and contribute to manuals and forms, obtain IRB approval, and be prepared to receive specimens from the Central Biochemistry Laboratory starting approximately January 1, 2020.

2. The laboratory should expect to receive and genotype DNA samples through the subsequent 24 months (Months 4-27). During the final 9 months (Months 28-36) the laboratory would prepare specimens for transmission to the NIDDK repository, conduct study close-out activities, and participate in manuscript preparation as appropriate.

3. Depending on the technological approach proposed, the budget may exceed the $500,000 (average per year) total direct costs allowed by NIH; however, prior approval by NIDDK would be needed before the grant application could be submitted.

The budget should be comprehensive and include all items required for the GRADE study. Cost to be budgeted by the CGL should include, but are not limited to the following:

- Personnel, fringe
- Electronic transfer of data to the Coordinating Center
- Equipment
- Storage
- Assay costs
- Travel costs for 2 persons to travel to the Washington DC area twice per year to attend GRADE Steering Committee meetings. Applicants should assume a two-night stay for each trip.
- Travel costs for 2 persons to travel to a scientific meeting at which the genomic study results are presented.
- Subrecipient costs: If any portion of the work is to take place at a lower-tier subrecipient, provide the same budget content for each organization as for the lead applicant.
- Indirect costs and other items as required

5.4.2 Budget

Applicants should submit the budget for the **3-year period October 1, 2019 through September 30, 2022** using the PHS 398 forms listed below with appropriate institutional signatures. Include additional spreadsheets detailing all budget costs including costs of each assay, as well as shipping, storage, and specimen supply costs. The components are:

a) Face Page
b) Detailed budget for Years 1-3
c) Summary budget page for Years 1-3
d) Detailed budget justification for Years 1-3
e) Checklist page
f) Third party subrecipient's information (if applicable). Provide same level of detailed information for each subrecipient
g) Copy of institution's rate agreement

5.4.3 Budget Justification

Applicants are required to submit a budget fully supported by cost and effort data adequate to establish the rationale for the proposed amounts. Justification information for all budget items in all budget periods should be provided in paragraph form following the budget pages. The justification must be broken down by the years of the study as outlined above. Detailed information must be included for all of the following:

1. Personnel: Identify positions by job title, and for key personnel, by individuals' names; indicate the effort to be devoted by each individual; by percentage or amount (days, hours) devoted to this project, and provide description of each individual's responsibilities on the project
2. Fringe Benefits: List the rates applied.

3. Equipment/Supplies: Justify necessity for all items. For equipment provide name, model number, and cost of proposed items. Similarly, indicate any rental or lease of equipment that is included in the budget.
4. Travel Costs *(see section 5.4.1 for more information)*
5. Subrecipients (if any): Provide justification for each organization as for the lead applicant. Include a signed letter indicating consent to enter into a subagreement with the proposed subrecipient for the GRADE Study.
6. Other and Unusual Costs: Any elements of direct costs not covered elsewhere shall be identified and explained.
7. F&A and other costs: If applicable, apply facilities and administrative (F&A), general and administrative (G&A), and/or fringe benefit rates to budget periods, as allowed by a federally negotiated rate agreement.

5.4.4 Current F&A and Fringe Benefit Rate Agreements

Provide a copy of your current federally negotiated F&A and fringe benefit rate agreement**.**

5.4.5 Other Administrative Data Terms and Conditions

The proposal shall stipulate that it is predicated upon all the terms and conditions of this Announcement. This subaward will be subject to the terms of the prime award including the NIH Grants Policy Statement. The proposal shall list the names, telephone numbers and email addresses of persons authorized to conduct negotiations and to execute subagreements.

The proposal shall contain a statement to the effect that the cost information is firm through October 1, 2019 start date. This Announcement does not constitute a commitment by The George Washington University or the NIDDK/NIH to the scope of work described, nor does it constitute a minimum scope of work under any resulting agreement. In addition, the Announcement may be amended or canceled as necessary to meet NIDDK's and the project's requirements.

No award will be issued in response to this Announcement. Rather, the application and the proposed budget will be employed in the preparation of a subsequent grant application to seek funding for these activities.

5.4.7 Other Important Cost Information

Costs should be listed in U.S. dollars. Note that a submission is no guarantee of funding or an award. Except for grants awarded under the SBIR/STTR programs, under an NIH grant, no profit or fee will be provided to a for-profit organization, whether as a grantee or as a consortium participant. A profit or fee under a grant is not a cost, but is an amount in excess of actual allowable direct and F&A costs. Since this project will be funded by a cooperative agreement (grant mechanism) and since the laboratory will be a subawardee/collaborator, a fee or profit is not allowed. For additional clarification, see NIH Grants Policy Statement Section 7.3 Direct Costs and Facilities and Administrative Costs.

6. TECHNICAL EVALUATION CRITERIA

Peer Review Process

A peer-review process will be used to evaluate the CGL applications. Applicants will be evaluated based on the following:

- Experience and expertise to serve as the CGL and to contribute as a collaborator with the GRADE Study Research Group;
- Technical ability to perform the genetic testing required to meet the study objectives, timely performance and reporting of assay results, and quality assurance monitoring/reporting;
- Adequacy of facilities and resources necessary, including IT resources, to provide genomic support services for the GRADE study;
- Adequacy of organizational and administrative structure and management plan for work coordination and timely delivery;

- Costs.

Proposals submitted in response to this announcement will be reviewed according to a two-stage process. The initial review will be conducted to evaluate completeness and responsiveness to the details of this Announcement. Incomplete proposals may be excluded from the full review process. After the initial review, proposals will be reviewed for scientific-technical merit by a group composed of senior GRADE investigators, in addition to experts in areas specifically relevant to the proposed activity. Technical evaluation criteria will receive paramount consideration in the selection. Evaluation will be based on demonstrated capabilities of the prospective organization in relation to the needs of the project as described in this Announcement. Cost effectiveness will enter into the overall evaluation.

During the initial review each proposal will be evaluated according to the following factors:

Factor (Weighting Percentage)

Technical Merit (55%)

Evidence of understanding the purpose of and need for the proposed undertaking and comprehension of issues relevant to accomplishing the objectives of the study; adequate attention paid to the proposal preparation requirements; knowledgeable assessment of the methodological problems posed by this undertaking and discussion of the means by which obstacles will be avoided, overcome, or minimized; ability to provide newer, potentially better measures or easier sampling systems; clarity of the subrecipient's proposed approach and the soundness, practicality, and feasibility of the plan for essential operations such as specimen labeling and handling, specimen processing and reporting throughput time, adequate internal and external quality control measures, and reporting of results; IT support and reporting capability to meet study needs; and adequacy of the facility including access to technical hardware, physical space, and storage capacity with appropriate power and alarm safeguards.

Personnel (25%)

Qualifications and experience of professional, technical, and administrative staff including: relevance of background in terms of professional credentials and administrative experience, including diversity of skills relevant to the proposed undertaking, and adequacy and appropriateness of time commitment of key staff members; quality of past work and extensiveness of experience performing related work; and experience of laboratory leadership in collaborating and communicating results with large study groups

Organization and Management (20%)

Adequacy of proposed organizational and administrative structure and discussion of the management plan to ensure work coordination and timely delivery; and evidence that the organization has undertaken high quality work of a similar nature (e.g., previous experience in serving as the CGL for collaborative clinical trials or other large-scale epidemiological or data collection activities that have required handling of this volume of specimens within the stated time frame).

7. SELECTION OF OFFEROR

Both the cost realism and technical merit of the proposal will be considered in making recommendations and selecting a proposal for award. During proposal evaluation paramount consideration will be given to the evaluation criteria (technical factors) as listed in this solicitation. Cost realism will enter into the overall evaluation process. However, the selection will not be made solely on the basis of lowest cost. Estimated costs must be reasonable for the tasks to be performed and if consideration is narrowed to choosing among proposals with

approximately equal technical factors, as determined by the evaluation, cost may become the determining factor.