

Pennsylvania Department of Health Final Performance Summary Report Formula Grants

Overview of the Health Research Project Performance Review Process and Criteria

An applicant that receives a health research grant under Tobacco Settlement Act / Act 77 of 2001, Chapter 9, is subject to a performance review by the Department of Health upon completion of the research project. The performance review is based on requirements specified by Act 77 and criteria developed by the Department in consultation with the Health Research Advisory Committee.

As part of the performance review process, each research project contained in a grant is reviewed by at least three experts who are physicians, scientists or researchers. Reviewers are from the same or similar discipline as the research grant/project under review and are not from Pennsylvania. Reviewers use the applicant's proposed research plan (strategic plan), the annual progress report and final progress reports to conduct the review. A grant that receives an unfavorable performance review by the Department may be subject to a reduction in funding or become ineligible for health research funding in the future. The overall grant evaluation rating is based on the ratings for the individual research projects contained in the grant.

This performance review report contains the outcome of the review for the grant as a whole (outstanding, favorable, or unfavorable), strengths and weaknesses of each research project, as well as recommendations for future improvement.

The following criteria were applied to information submitted by research grant recipients:

- **Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?**
 - Did the project meet the stated objectives?
 - Were the research design and methods adequate in light of the project objectives?
 - Consider these questions about data and empirical results: Were the data developed sufficiently to answer the research questions posed? Were the data developed in line with the original research protocol?
 - If changes were made to the research protocol, was an explanation given, and, if so, is it reasonable?
 - Consider (only for clinical research projects) the extent of laboratory and clinical activities initiated and completed and the number of subjects relative to the target goal.
 - Were sufficient data and information provided to indicate or support the fact that the project met its objectives or made acceptable progress?
 - Were the data and information provided applicable to the project objectives listed in the strategic research plan?

- **Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?**
 - What is the significance of this project for improving health?
 - Consider the value of the research completed towards eventual improvement in health outcomes.
 - Consider any changes in risk factors, services provided, incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of impact and effectiveness of the research being conducted.
 - Consider any major discoveries, new drugs and new approaches for prevention, diagnosis and treatment, which are attributable to the completed research project.
 - What are the future plans for this research project?

- **Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?**
 - If leveraging of funds were expected, did these materialize?
 - Are the researchers planning to apply for additional funding in the future to continue or expand the research?

- **Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted/filed?**
 - If any of the above listed were expected, did these materialize?
 - Are the researchers planning to submit articles to peer-reviewed publications, file for any licenses, or patents or begin any commercial development opportunities in the future?
 - Consider the number/quality of each.

- **Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?**
 - Were there improvements made to infrastructure?
 - Were any new investigators added or were any researchers brought into the institution to help carry out this research?
 - Were funds used to pay for research performed by pre- or post-doctoral students?

- **Criterion 6 - Did the project lead to collaboration with research partners outside the institution, or new involvement with the community?**
 - Are the researchers planning to begin any collaborations as a result of the research?
 - For clinical research only: consider the number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the Commonwealth.

Overall Evaluation Rating

An overall evaluation rating is assigned to each research project. The rating reflects the overall progress the project attained in meeting the stated goals and objectives. The rating is based on a scale of 1–3, with 1 being the highest. An average rating is obtained from all the reviews (minimum of 3) of each project and is the basis for the determination of the final overall rating for each project as follows:

1.00 – 1.33 = *Outstanding*

1.34 – 2.66 = *Favorable*

2.67 – 3.00 = *Unfavorable*

The grant level rating is an average rating from all projects as above. The numerical rating appears in parentheses for the grant and each project in the ***Overall Grant Performance Review Rating*** section of the report.

Overall Grant Performance Review Rating

Grant Rating: Favorable (2.00)

Project Rating:

| Project | Title | Average Score |
|----------------|---|----------------------|
| 0990201 | Fine Mapping of Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes | Favorable (2.00) |

Project Number: 0990201
Project Title: Fine Mapping of Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes
Investigator: Lonsdale, John

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The purpose of this project titled, “Fine Mapping of Genetic Susceptibility for Microvascular Complications in Patients with Type 1 Diabetes (T1D),” was to identify specific genes responsible for diabetes complications such as retinopathy, nephropathy, and neuropathy. The specific aims of this project were: 1) to analyze the existing single nucleotide polymorphisms (SNP) data using case-control association tests; 2) to genotype representative SNPs on new members selected from the Human Biological Data Interchange (HBDI) families to perform family-based association and linkage analyses and confirm the results from the case-control association analysis; 3) to continue the annual program of participant follow-up using an updated family questionnaire to track any development or progression of microvascular complications among patients with both T1D and T2D to enhance the sample size and maintain the scientific value of the dataset; and, 4) to plan and execute analysis of any other genomic region of interest found to be important in the development of retinopathy in the HBDI patients with T1D.

Strengths: In this study, investigators met all the objectives reasonably well. Although the data generated sufficiently answered the questions, given the ongoing nature of the study, (especially for Aim 3) it is hard to measure how best the aim was fulfilled. Nevertheless, this effort seems to be successful because annual updates have led to a significant rate of follow-up visits to monitor or track development/progression or lack of development/progression of complications. Thus, the study design and methods appear to be appropriate to address the project objectives. Considering the data presented and results reported, this project has made acceptable progress. No changes were made to the initial study design.

Weaknesses: The study is a little confusing and complicated, since the goal was to deal with a number of complications relating to both type 1 and type 2 diabetes. It is not clear as to why to include type 2 diabetes when the purpose of the study was primarily to study the complications of type 1 diabetes. Furthermore, it is not clear if there is enough power in sample sizes of 38 (retinopathy) and 31 (neuropathy) for the case-control association tests. If the p-values reported as part of Specific Aim 1 were adjusted for multiple testing, it would be helpful to report them as well. In the fourth specific aim, the context or significance of focusing on retinopathy is not clear, and the saturation study association analysis results are not reported.

Reviewer 2:

There are indeed strengths and weaknesses to this study. The actual results seem rather limited as far as validating the association of genetic variants with microvascular complications. It is disappointing that the final analysis had not been completed at the time of the progress report. This disappointment should be viewed in the context of the overall funding for several years having been very modest in scope, and expectations for a higher visibility result would have been unrealistic.

The funds for this grant helped support continued contact with the Human Biological Data Interchange (HBDI) study sample-- a unique resource for researching type 1 diabetes. The continued contact and monitoring of subjects from the database provides great value for future research into the complications of type 1 diabetes.

Reviewer 3:

The global goal of the proposal was to identify genes contributing to diabetic complications. Three aims were proposed. The study was for only one year. It appears that the investigators addressed all three aims identified in the proposal.

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The clinical and familial data contained in the Human Biological Data Interchange (HBDI) database is an invaluable resource for the development and testing of hypotheses regarding genetic factors leading to susceptibility to diabetic complications. Since diabetes complications cause the biggest toll on the lives of diabetes patients, it is very important to address the genetic basis of such complications. Furthermore, improved methods of preventing, treating, and curing diabetes will inevitably stem from a more thorough determination of which specific genetic factors contribute to the development of diabetic complications. This study has shown that some families with type 1 diabetes (T1D) are more susceptible to developing complications than others. Also, some of the genes that potentially play a role in the susceptibility to T1D have already been identified in this study. Thus, this project is significant because the identification of type 1 diabetics who are genetically susceptible to retinopathy, neuropathy, and nephropathy is of considerable benefit to subjects and society as well. More importantly, these findings will help formulate better preventive and treatment measures and improve health outcomes.

As for the future plans of this project, investigators are proposing to continue to explore the genetic contributions to the development of complications in individuals with diabetes-- exploring the availability of confirmation datasets with similar data points and DNA availability to confirm their previous report on significant single nucleotide polymorphisms (SNPs) demonstrated to be protective to the development of complications. Additionally, with this year's grant they are proposing to examine functional differences from normal retinas, diabetic normal retinas and diabetic retinopathy affected retinas. This work will not only provide functional confirmation of the importance of the SNPs demonstrated to be protective from their previous

analysis, but will lead to potentially additional genetic targets to explore. Also, plans are in place to continue family follow-up on a yearly basis to obtain vital information, including new family members, newly diagnosed individuals with diabetes (type 1, type 2 and monogenic forms), and development or absence of complications.

No major discoveries, new drugs, or new approaches for prevention, diagnosis, and treatment that were attributable to the project are reported.

Reviewer 2:

The major beneficial impact, as described above, is the continued development and support of the Human Biological Data Interchange (HBDI) database through contact with subjects and families and continued recruitment to the database. This is effectively an infrastructure development that should continue to pay dividends in the future. The modest funds available could effectively support this effort.

The primary aim of the grant, to identify genetic variants that are associated with microvascular complications of type 1 diabetes, does appear to have been successful-- or at least at this time as it has not been completed. Realistically, given the funds available, achieving substantial success with this aim would have been unexpected given the effort it supported.

Reviewer 3:

Diabetic complications are the reason for diabetes related mortality and morbidity. Identification of genes responsible for specific complications will have a huge impact on how we identify patients for prevention and treatment.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Additional acquisition of funds is expected through this project. The investigators are planning to submit a proposal for the Type 1 Diabetes Impact Award (DP3) with collaborators at Columbia University. It is possible that National Disease Research Interchange will provide subcontract support for this proposal. The proposal may fund their work exploring the genetic contributions to the development of complications in individuals with diabetes.

Reviewer 2:

The project did not leverage additional funds. An R21 application was submitted to NIH but was unsuccessful. In order to be competitive in the national funding arena, a genetic study will have to take full advantage of the resource of the Human Biological Data Interchange (HBDI) to have adequate power. Ultimately there are limitations--the number of subjects from HBDI with documented microvascular complications is modest, so alone it may not be adequate to power an overall study. It does not appear that that investigators plan to submit additional grants.

Reviewer 3:

No proposals were submitted during this period. It was stated that a proposal was in preparation to be submitted to NIH in collaboration with Columbia University. This was a special call from NIH entitled Type 1 Diabetes Impact Award, and the project was perfect for this call. The results of the review process were recently made available to the applicants. It would be interesting to see how this application was received if submitted.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Investigators are planning to submit an article for publication to a top tier journal detailing their findings on the role of specific single nucleotide polymorphisms (SNPs) within this chromosomal region in either protection from or contribution to the development of retinopathy related complications of type 1 diabetes (T1D) at the conclusion of the data analysis. Also, depending on the outcome of the data, additional articles may be submitted for publication.

Reviewer 2:

The project apparently did not result in any peer-reviewed publications or abstracts. From this perspective, it was disappointing. No licenses, patents, or commercial applications were developed from this work and seem unlikely in the future.

Reviewer 3:

The investigators state that results are being analyzed for manuscript submission. The last paper published by the principal investigator was in 2007.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:

This project has slightly enhanced the capacity of research at their institute. One undergraduate student and one pre-doctoral student received funding support.

Reviewer 2:

The near-term impact of this research was limited, as noted above. The greatest value was to continue the maintenance of the HBDI infrastructure; in this case, this would have to be considered the greatest positive for the project. It did connect the investigators with Dr. Monti at Columbia and did involve some training of a pre-doctoral student. These were modest accomplishments but were noted.

Reviewer 3:

One graduate student and one undergraduate student were involved in the project; but, as indicated by the PI, the project did not enhance research at the affiliated institution.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The investigators developed collaboration with the University of Pennsylvania's Microarray and DNA Sequencing Facility. This facility carries out all sequencing and microarray work. In addition, in view of their interest in growing the National Genetics Family Registry to provide additional families eligibility to enroll in these studies, they have continued to reach out to the community.

Reviewer 2:

It is not apparent that new collaborations will develop from this effort. The HBDI sample would seem most effectively used as part of a broader consortium that would be better powered.

Reviewer 3:

The principal investigator established collaboration with the sequencing facility. Also, the project requires community involvement, and investigators recruited new families to the project.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

1. The scope of the project is too broad. It would be ideal if the focus were narrowed down to one complication at a time while adjusting for the effects of other correlated traits or complications.
2. In Aim 3, "continue the annual program of participant follow-up using an updated family questionnaire to track any development or progression of microvascular complications among patients with both T1D and T2D to enhance the sample size and maintain the scientific value of the dataset," it is not clear how type 1 and type 2 diabetic subjects are going to be analyzed. It may be helpful to provide more details on this.
3. In association studies, replication of a disease association in one or more samples is very critical for publication, so is there any plan to conduct replication analysis?

Reviewer 2:

1. The major weakness, as outlined above, is still recoverable by delivering a final analysis of the data that was acquired, which would enable an assessment of whether there would be a future for this work.

2. It seems likely that the dataset would be most useful in meta analysis with other similar efforts-- this should be encouraged.
3. The greatest value is the HBDI resource. A plan for its continued support and expansion would give some hope for the future of the project.

Reviewer 3:

From a clinical standpoint, the project is highly significant, since it focused on diabetic complications.

Recommendation: The outcome and results of this important project should be published and further expanded in new proposals supported by strong and compelling data obtained by this pilot study. If the results are not published and shared with the scientific community to advance the field, all the work that has been done is futile and funds were misspent.

ADDITIONAL COMMENTS

Reviewer 2:

Again, reflecting upon the limitations of the modest budget, the investigators did not come to a final analysis that provided much insight into the genetic basis of diabetic microvascular disease, nor development grants or further interactions that could have developed out of this study. Training was limited and not very positive. The continued support of the HBDI sample is the real positive.