Response Form for the Final Performance Review Report—
Geisinger Clinic-Weis Center for Research 2008F*

1. Name of Grantee: Geisinger Clinic-Weis Center for Research

2. Year of Grant: 2008 Formula Grant

A. For the <u>overall grant</u>, briefly describe your grant oversight process. How will you ensure that future health research grants and projects are completed and required reports (Annual Reports, Final Progress Reports, Audit Reports, etc.) are submitted to the Department in accordance with Grant Agreements? If any of the research projects contained in the grant received an "unfavorable" rating, please describe how you will ensure the Principal Investigator is more closely monitored (or not funded) when conducting future formula funded health research.

Since this grant project was completed, the research administrative structure at Geisinger Clinic has been expanded and enhanced. A Chief Scientific Officer was recruited in 2011, who has overall executive responsibility for research programs within the Geisinger Health System. The Office of Sponsored Projects and the Research Compliance Office have also been expanded and reorganized. These offices are responsible for ensuring that legal and regulatory aspects of external grants and research contracts are met. A system-wide Research Compliance Committee has also been formed. Finally, the external Scientific Advisory Board has been expanded. This group provides strategic oversight of Geisinger research programs, as well as rigorous and objective evaluation of externally funded projects.

For <u>each research project</u> contained in the grant, please provide a response to items B-D as listed on the following page(s). When submitting your response please include the responses for all projects in one document. The report cannot be submitted as a ZIP file, because the Department's exchange server will remove it from the email. If the report exceeds 2MB, please contact the Health Research Program for transmittal procedures: 717-783-2548.

* Please note that for grants ending on or after July 1, 2007, grantees' Final Performance Review Reports, Response Forms, and Final Progress Reports ***will be made publicly available on the CURE Program's Web site.***

Project Number: 0863501
Project Title: Genomics of Pregnancy-Related Complications
Investigator: Carey, David

B. Briefly describe your plans to address <u>each</u> specific weakness and recommendation in Section B using the following format. As you prepare your response please be aware that the Final Performance Review Report, this Response Form, and the Final Progress Report will be made publicly available on the CURE Program's Web site.

<u>Reviewer 1:</u>
The investigators have developed a useful tissue bank for perinatal research. However, a clear research focus needs to be developed using these materials.

Response: We agree that the tissue bank is a valuable resource that could drive important research. The development of the biobank and its research uses to date were presented recently to a newly formed Women's Health Research Committee at Geisinger. This group discussed various ideas on how to expand the biobank and specific research priorities for its future use.

<u>Reviewer 2:</u>
1. The investigators need to focus on extreme phenotypes when evaluating genetics. In this regard, focusing on early onset preeclampsia would have been ideal, as these subjects have the greatest morbidity.

Response: The reviewer is correct that extreme phenotypes can be extremely valuable for genetic studies. In the future as the biobank expands and the available sample size increases it will be informative to view early onset preeclampsia as an extreme phenotype for genetic studies.

2. Ethnicity and race were not discussed in the application. If the subjects were predominantly white or black, that would have significantly affected the genetic studies.

Response: The Geisinger Clinic patient population is 96% White-caucasian, with African American and Hispanic patients representing less than 2% each. We are aware that ethnicity and race must be accounted for in genetic studies due to population differences in the frequencies of specific genetic variants. Population stratification was not a factor in the current study.

3. No plan is provided with regards to follow-up of the microRNA work. Are they planning to do validation and functional studies?

Response: Future follow-up studies will include pathway network analysis, bioinformatics analysis of target gene sequences, analysis of expression of target genes in placental tissues from preeclampsia and normal deliveries, and cell culture studies to investigate miRNA function.

4. The plans for preterm labor were not clearly outlined in the proposal.

Response: The main objective of the project was to study preeclampsia. Preterm labor patients were also enrolled and tissue was collected for the biobank to provide a resource for future studies of pregnancy complication, when the sample size reached an adequate size.

<u>Reviewer 3:</u>

1. The investigators should consider adding epidemiologic support to the project to determine the accuracy and completeness of the electronic medical record data, the denominator from which findings can be generalizable, and the nature of bias in study population selection, including those emerging from high-risk referral patterns into the obstetrics facility, from retrospective recruitment (parity effects), from differential follow up, etc.

Response: Since this project was completed, we have gained considerable experience in mining electronic medical record data for epidemiologic studies. This includes developing algorithms and procedures for creating reliable and accurate phenotypes from electronic medical record data, and analyzing population level variables and risk factors. These types of analyses are being added to the study.

2. If a sufficient number of study subjects continues to hamper the conduct of single-nucleotide polymorphism (SNP) analyses in this project, the investigators should continue to look at novel approaches (e.g., trios), different tissue types (e.g., placenta, amniotic, vaginal), lab analyses (e.g., comprehensive sequencing, proteomics) and other hypotheses to test.

Response: We are investigating multiple alternative approaches, including retrospective and prospective recruitment of trios for genetic studies, use of next generation DNA sequencing, and other approaches to obtain DNA samples to increase the sample size.

3. The investigators should consider that the strengths of the Geisinger Clinic setting for research may be in the depth of laboratory analysis, breadth of exploration, and in its patients' long-term stability, not so much in its being population-based, and revise their research goals appropriately.

Response: We have invested considerable resources into utilizing longitudinal electronic medical record data on Geisinger patients for clinical translational research. As the reviewer points out, such data is typically much broader than what would normally be obtained in a typical research study, which can substantially expand the breadth of research questions to be addressed. The stability of the Geisinger population and integration of the Geisinger health care system are highly favorable for the collection and analysis of longitudinal data. Such studies are becoming increasingly important in our research strategy.

C. If the research project received an "unfavorable" rating, please indicate the steps that you intend to take to address the criteria that the project failed to meet and to modify research project oversight so that future projects will not receive "unfavorable" ratings.

Response: N/A.

D. Additional comments in response to the Final Performance Review Report (OPTIONAL):

Response: None.