

## **Response Form for the Final Performance Review Report\***

1. Name of Grantee: Children's Hospital of Philadelphia
2. Year of Grant: 2008 Non-Formula Grant
3. Project Title: CHOP/Penn Center of Excellence for Autism Research
4. Principal Investigator: Robert T. Schultz, PhD

### ***A. Briefly describe your plans to address each specific weakness and recommendation in Section B of the Final Performance Review Report using the following format.***

Reviewer Comment on Specific Weakness and Recommendation (*Copy and paste from the Final Performance Review Report the reviewers' comments listed under "Section B - Specific Weaknesses and Recommendations"*):

#### Reviewer 1:

1. There were essentially no results presented for either Project 4 or Project 5. While it is appreciated that the recruitment and imaging was a major undertaking, there appeared to be little effort placed in analyzing the acquired data in real time. One concern is that there may have been a systematic problem in some aspect of the data collection which would only be appreciated after the project was over and not allowing for any mid-course corrections. These projects should be completed and the data presented in peer-reviewed publications.
2. It would be excellent to see further integration between the genetic data of Project 2 with the neuroimaging data of Project 4.
3. The real benefit of this first 4 year project will be the usefulness of the resource over the next several years. I would encourage the investigators to reach out to investigators even beyond their institution to analyze the neuroimaging and genetic databases that have been acquired.

#### Reviewer 2:

None.

#### Reviewer 3:

1. The oversight with regards to the figures in the report is concerning. When I see utter failure to proofread a final document like this it always brings up questions for me about how thorough the investigators are in other aspects of the scientific enterprise. In the future, the investigators should be more attentive to the final product.
2. The most significant weakness across the projects is the fact that data collection and management has filled the entire project period, leaving many of the planned analyses unfinished at the time of the report. Although there is substantial record of productivity in publications that use parts of the dataset or that report methods development that will be applied to the dataset, it will be important to see the results of the planned analyses in the final sample to assess the success of the project.

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

3. The investigators appear unwilling to consider alternatives to the social motivation hypothesis of autism (see above). It is important for negative results to be acknowledged and alternative explanations to be considered for the observed data.

Reviewer 4:

There was no major weakness noted for the overall progress of the Center. The next step would be to translate knowledge gained from this study into clinical practice or to develop effective treatments. There are minor concerns with individual projects (see above), in which efforts need to be made to accomplish the original goals.

Reviewer 5:

There were no clear major weaknesses noted. The animal work needs completion on some tests given the delay in model development.

Reviewer 6:

Many of the unmet objectives were supplemented by additional research goals. Although these goals were worthwhile and resulted in advancements in knowledge and publications, the investigators are encouraged to further pursue studies in line with original study objectives where applicable and possible.

Reviewer 7:

None.

Response (*Describe your plan to address each specific weakness and recommendation in ongoing or future research funded by the Health Research Program*):

Reviewer 1 stated that, “There were essentially no results presented for either Project 4 or Project 5”. This comment puzzles the Researchers as the final progress report contained 13 pages of detailed results for Project 4 and 21 pages of detailed results for Project 5. For Project 4, the final progress report also listed 5 published papers, 4 papers under review, and 13 conference presentations. For Project 5, the final progress report listed 9 published papers. Since submitting the final progress report, the Researchers have published 3 more papers from Project 4 and 5 (for a total of 17 published papers across those 2 projects):

1. Kerns, C. M., Kendall, P.C., Berry, L., Souders, M. C., Franklin, M. E., Schultz, R. T., Miller, J., & Herrington, J. Traditional and atypical presentations of anxiety in youth with autism spectrum disorder. Journal of Autism and Developmental Disorders. In Press.
2. Granader, Y, Wallace, GL, Hardy, KK Yerys, BE, Lawson, RA, Rosenthal, M, Wills, MC, Dixon, E, Pandey, J, Penna, R, Schultz, RT, & Kenworthy, L. Characterizing the Factor Structure of Parent Reported Executive Function in Autism Spectrum Disorders: The Role of Cognitive Inflexibility. Journal of Autism and Developmental Disorder, In Press
3. Tunc, B., Ghanbari Y, Smith, A.R. Pandey, J. Browne, A., Schultz, R.T., Verma R. PUNCH: Population Characterization of Heterogeneity. Neuroimage, In Press

The Researchers agree with Reviewer 1 that it “would be excellent to see further integration between the genetic data of Project 2 with the neuroimaging data”. Indeed, those analyses are underway. As many of the Reviewers noted, this Center Grant yielded an enormous amount of data and the Researchers expect to continue to publish new results from this dataset for the foreseeable future. The Researchers also agree with the final comment from Reviewer 1: “The real benefit of this first 4 year project will be the usefulness of the resource over the next several years. I would encourage the investigators to reach out to investigators even beyond their institution to analyze the neuroimaging and genetic databases that have been acquired.” The

Researchers have begun to do exactly this, and they expect that this line of work will be central to new grant applications and future research at the CHOP/UPENN Center for Autism Research.

The Researchers also agree with Reviewer 3 that a project weakness was “the fact that data collection and management has filled the entire project period, leaving many of the planned analyses unfinished at the time of the report”. Similar points were made by other reviewers including Reviewer 1 who noted, “very little integration of data across projects to answer questions such as the genetic basis of certain patterns of altered brain development”; Reviewer 6: “the investigators are encouraged to further pursue studies in line with original study objectives where applicable and possible”; and by Reviewer 4, who noted “minor concerns with individual projects, in which efforts need to be made to accomplish the original goals”. Finally, Reviewer 5 noted that the “animal work needs completion on some tests given the delay in model development”. The Researchers agree with each of these comments. With respect to the animal studies in Project 2, work has been ongoing, and in fact, 2 new papers have recently been submitted for publication. In summary, while many papers have been published, work continues, and the Researchers intend to complete all planned analyses, including the integration of data across projects. This is a very rich data set that permits numerous interesting hypotheses to be tested. The Researchers are eagerly pursuing each of them.

Reviewer 3 suggested that there was an “utter failure to proofread the final document” which raised questions “about how thorough the investigators are in other aspects of the scientific enterprise”. Specifically Reviewer 3 identified problems with some of the figures in the document that the Reviewer received, since the figures apparently occluded text in various places in the final document. This comment was surprising because the Researchers were fastidious in their preparation of the final report. Moreover, the Researchers have now verified that there were no formatting issues or errors or any kind in the document that they submitted to their Grants and Contracts office for transmittal to the State. The Researchers have consulted about this matter with the Pennsylvania State Department of Health who indicated that corruption was likely introduced by the file transmission process itself. Unfortunately, the transmitted Microsoft Word (per State requirements) document was 118 pages long with more than 40 figures, and Word can be very temperamental about the placement of figures on a page. There was no way for the Researchers to know that errors were introduced after it left their hands. This is unfortunate, as a tremendous amount of effort was put into this very detailed and carefully prepared document, so as to provide the Reviewers with a complete representation of the substantial progress and accomplishments from this Center grant.

The Researchers disagree with Reviewer 3’s comment that the “investigators appear unwilling to consider alternatives to the social motivation hypothesis of autism”. In the main body of the performance evaluation, Reviewer 3 more specifically suggested that intact social motivation in person with ASD could explain the lack of an “audience effect” that was found in one of the Researcher’s publications (Chevallier, et al, 2014, Susceptibility to the audience effect explains performance gap between children with and without autism in a Theory of Mind task. Journal of Experimental Psychology: General). While the Researchers agree with Reviewer 3 that social motivation is merely a heuristic model and that not all individuals with ASD have low social motivation, the Researchers and the peer reviewers of this paper agreed that impaired social motivation was a reasonable explanation for these findings. Since Reviewer 3 did not further clarify how intact social motivation in person with ASD could explain the lack of an “audience effect”, the Researchers cannot determine if there is a more nuanced point to consider. The Researchers welcome all evidence that moves the field forward, regardless of their current or prior hypotheses.

Finally, Reviewer 4 notes that, “The next step would be to translate knowledge gained from this study into clinical practice or to develop effective treatments.” The Researchers agree that this is the ultimate goal and the ultimate purpose of all of this research. However, this is a very high bar to set for any one project, as the field has collectively been working toward this goal for many years. Although it is critically important to have this goal clearly in mind when conducting the kind of research focused on in this Center grant, the Researchers believe that this Reviewer’s comment fails to describe the incremental nature of science. Rarely if ever does one project or one set of projects allow immediate and tangible changes in clinical practice, even though that is always the hope. More often it is the cumulative increase in knowledge across many studies, across many years that allows this type of tangible progress. Nonetheless, as the Researchers complete final analyses of every facet of this work, this will be the goal that the Researchers strive to achieve.

***B. If the grant received a rating of “unfavorable,” please indicate the steps that you intend to take to address the criteria that the project failed to meet, and to modify the grant oversight process so that future projects will not receive “unfavorable” ratings.***

Response: This grant received an “Outstanding” rating.

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

Response: None