

# 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 (2.17)

**Project Rating:**

<b>Project</b>	<b>Title</b>	<b>Average Score</b>
0863301	Investigation of the Hepatitis C Virus 3'-Untranslated Region, as a Potential Target for new Antiviral Nucleic-acid-based Strategies	Favorable (2.00)
0863302	Impact of Parental Smoking Cessation and Residential Hazard Reduction on Pediatric Respiratory Health: A Pilot Investigation	Favorable (2.33)

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**Project Number:** 0863301  
**Project Title:** Investigation of the Hepatitis C Virus 3'-Untranslated Region,  
as a Potential Target for new Antiviral Nucleic-acid-based Strategies  
**Investigator:** Mihailescu, Mihaela

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## ***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:

**Strengths:** The overall idea of developing peptide nucleic acid based aptamer to inhibit hepatitis C virus (HCV) replication by disrupting the RNA-RNA interaction is novel. If this becomes successful it may lead to a novel antiviral strategy for chronic HCV infection. Some of the initial observations made during the previous funding are interesting and important in understanding the RNA-RNA interactions involved in HCV replication. Some of the molecular studies performed *in vitro* are very impressive and convincing.

#### Specific Aim 1:

1. The group provided evidence that the 55nts 3'UTR segment representing the stem-loop 2 and 3 form two different monomeric conformations (I and II), which supports the structures obtained by mfold computer software.
2. The group showed that 48nt HCV RNA corresponding to the NS5B coding region (9263-9310) interacts with one conformation and the other conformation of the 55nts 3'UTR engages in homodimer formation.
3. The NS5B (48nt) and 3'UTR (55nt) kissing interaction is prevented in the presence of HCV core protein, whereas the X55-X55 homodimerization become more stable in the presence of core protein.
4. The group has determined the dissociation constants of these two interactions by using fluorescence microscopy. They found that X55-NS5B interactions have dissociation constant (42+6nM) and X55-X55 homodimers have dissociation constant (Kd=318+58nM). This means the NS5B-X55 interaction is stronger than the X55-X55 homodimerization.
5. The study has provided evidence indicating that the stem-loop III<sub>d</sub> region of HCV 5'UTR also interacts with the HCV NS5B region and this interaction is not affected by HCV core protein.

#### Specific Aim 2:

1.10 base peptide nucleic acid (PNA) was designed against X55 3'UTR in collaboration with Danith Ly of Carnegie Mellon University. When the PNA was added to X55 RNA it prevented homodimerization and kissing interaction with NS5B RNA. They also show dose-dependent inhibition of kissing interaction of X55 and NS5B.

The PI has achieved the two objectives as they were proposed originally. The methodology used in the progress report is based on examining the RNA-RNA interaction using fluorescence microscopy and gel electrophoresis.

**Weaknesses:**

- Only one publication and one review article were published during the last three years.
- The progress has been slow in this project.
- The competition experiments using PNA to inhibit the RNA-RNA kissing interactions are not very convincing.
- The antiviral strategy of PNA has not been tested in HCV cell culture model.

**Reviewer 2:**

Dr. Mihailescu proposed two specific aims in the original application, including: 1) molecular characterization of the long-range RNA-RNA interaction between the kissing-loop within the hepatitis C virus (HCV) 3'-untranslated region (3'UTR) and the coding region for the C-terminal NS5B (5BSL3.2); and, 2) screening for nucleic acid aptamers that block the above-described long-range RNA-RNA interaction. Using an *in vitro* gel electrophoresis assay, the PI completed the proposed studies to dissect different moods of RNA-RNA interactions in the presence or absence of HCV core protein/peptide, MgCl<sub>2</sub>, and different temperatures. Results derived from these studies suggest that the long-range RNA-RNA interaction between the 3'UTR kissing-loop and 5BSL3.2 exists, consistent with the findings obtained from genetic studies reported by others. Therefore, most of the studies proposed in Aim 1 were completed. As expected, the long-range interaction between the 3'UTR kissing-loop and 5BSL3.2 was blocked by a synthetic peptide nucleic acid (PNA) aptamer *in vitro*. Therefore, the studies described in both specific aims are considered largely completed.

**Reviewer 3:**

The project proposed to investigate the presence of certain secondary and tertiary structures involving an extremely well-conserved region of the hepatitis C virus 3'-UTR, and to assess whether it would be possible to disrupt these interactions by using oligonucleotide therapeutics. More specifically, the PI proposed to characterize a long-range, so called 'hairpin kissing' interaction between the absolutely conserved X RNA region within the 3'-UTR and the region coding for NS5B. In the course of this project, the investigators demonstrated that a conserved region within the X-RNA of about 55 nucleotides contains all the functional requirements of the entire element. They characterized the monomer-dimer equilibrium within the X RNA, and a second structure that forms, in equilibrium with the intramolecular structure, through an interaction with the NS5B sequence. They went on to demonstrate that both interactions are kissing hairpins that form in a magnesium dependent manner. These results led to the very reasonable suggestion that these interactions could function as a molecular switch, which would be well worth targeting with antivirals, since these sequences are essential for the viral lifecycle and extremely well conserved.

In the second part of the project, they investigated whether it would be possible to block this critical interaction with oligonucleotide analogs (PNA) directed against this critical region of the viral RNA. They screened for aptamers that block formation of the intermolecular kissing

complex and provided evidence that it is indeed possible to disrupt this interaction *in vitro* using PNA chemistry, thereby accomplishing the goals of Aim 2 as well as Aim 1.

***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:

Strengths: Development of PNA to inhibit HCV replication is important. This can be used to treat chronic HCV infection.

Weaknesses: Treatment of chronic HCV infection with interferon-alpha, ribavirin and protease inhibitors has been very good. There is hope that treatment of chronic HCV infection with the combination of new antiviral drugs will be better. The use of PNA approach to treat chronic HCV infection may not be useful, since there are so many new drugs that are currently in phase I and phase II trials.

The project seeks to develop PNA focusing on one target. It is possible that long-term treatment using a single agent could result in the development of escape mutants. There is no future plan for minimizing escape variants.

Also what will they do if this PNA antiviral approach does not work in HCV cell culture model? Delivery of PNA to infected liver cells also will be challenging.

Overall, there are numbers of important issues that need to be resolved in the proposed antiviral approach. Considering all these weaknesses, the chance of success in this project is low.

#### Reviewer 2:

Findings derived from the studies proposed in this application provide additional evidence to support the previous reports by others that the RNA-RNA interaction between the 3'UTR kissing-loop and 5BSL3.2 is important for HCV RNA replication. Additionally, the proof-of-concept was demonstrated that a PNA aptamer is able to block the kissing-loop and 5BSL3.2 interaction. However, the potential application of PNA to antiviral intervention has not been validated.

#### Reviewer 3:

The value of the project resides in identifying the biochemical characteristics of intramolecular interactions formed by exceptionally conserved and functionally essential regions of the Hep C RNA. This knowledge is a prerequisite for targeting these conserved structures with new antivirals. There were no new drug discoveries, and none should have been expected given the time frame of the project and resources available, although there is the possibility to develop a useful approach with possible commercial value for the longer term. The investigator has applied to NIH for support, using data resulting from this award.

***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:

Strength: The project was funded by Ruth L Kirschstein National Service Award (\$62,031) in 2011.

Weakness: This project did not receive national funding such as NIH or National Science Foundation.

Reviewer 2:

A small fellowship grant was awarded to support the proposed studies during the funding period of this application. Additionally, the PI has submitted two grants to NIH and National Science Foundation to continue or expand the studies described in this application.

Reviewer 3:

The investigator has applied to NIH for funding. The support must have undoubtedly been beneficial to apply for these funds, without which it is doubtful that significant preliminary results would have been available, regardless of the ultimate outcome. A post-doctoral National Research Service Award was granted around this project.

***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:

Strength: There was one publication in a peer-reviewed journal and one review article.

Weaknesses: The productivity was low.

Reviewer 2:

Two excellent publications in *RNA* and *Nucleic Acids Research* resulted from the studies proposed in this application. However, there is no intellectual property, patent, license, or commercial development opportunity that arose from the outcomes of this application.

Reviewer 3:

Two publications have been completed; one has already been published in a high-quality journal (*RNA*) and a second is under review at *Nucleic Acids Research*.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

Strength: The project supported one undergraduate and one graduate student.

Weakness: There is no evidence that they have recruited any new researcher or new investigator using the resources.

Reviewer 2:

There was no significant impact on the quality and capacity for research at the PI's institution.

Reviewer 3:

It does not appear that any significant improvement was made in regards to infrastructure. However, funds were used to support a pre-doctoral student.

***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:

Strength: There is evidence of collaboration with Stanley Lemon at the University of Texas at Galveston and collaboration with Dr. Danith Ly at Carnegie Mellon University.

Weakness: None

Reviewer 2:

This application resulted in productive collaborations with Dr. Danith Ly at Carnegie Mellon University and Drs. Yan Yang, Lishan Su, and Stanley Lemon at the University of North Carolina at Chapel Hill.

Reviewer 3:

Collaborations were established with a very strong virology group (Lemon at UNC) to conduct validation of the work conducted *in vitro* and with Ly at Carnegie Mellon University for the PNA chemistry.

## ***Section B. Recommendations***

### **SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

#### Reviewer 1:

1. Development of a PNA based antiviral approach based on RNA base pairing or kissing interaction between two RNA domains is not a very attractive antiviral strategy. The project is at a very early stage of development. The overall enthusiasm for this project is low because there is no cell culture data available to evaluate how effectively this antiviral strategy will block HCV replication.
2. The prospects of treating HCV infection with small molecule drugs targeting the viral polymerase, protease and NS5A are good. The cure rate of chronic HCV infection using triple combination therapy has been improved significantly. It is also expected that the response rate will be higher with newer antivirals targeting the NS5B and NS4A. It is not clear how effective this PNA based antiviral strategy will be. There will be an issue of inhibiting HCV RNA by PNA by avoiding cellular cytotoxicity. There are a number of issues that need to be addressed in case this PNA based antiviral approach is developed against HCV.
3. Another challenge will be how to deliver this PNA to the infected cells in the liver.
4. The PI has not developed this project rigorously to make a strong case that this antiviral approach inhibits HCV replication. Most of the work during the last three years has been focusing on determining the RNA-RNA interaction and designing PNA. The PI has selected only one target. What will they do if this approach or target is not effective or in case HCV develops resistance to this target?
5. The PI did not provide a realistic plan for how she will succeed in developing an antiviral strategy against HCV using the novel peptide nucleic acid drugs. At present there is less enthusiasm about the overall success of this project.

#### Reviewer 2:

1. The long-range RNA-RNA interactions between the 3'UTR kissing-loop and the NS5B-coding region need to be confirmed structurally by enzyme digestion and/or NMR studies. NMR studies proposed in Aim 1 should be pursued in future studies in order to validate the RNA structures.
2. The inhibitory activity of the PNA tested in vitro appeared to be weak. The PI should continue the screening for additional PNA aptamers as proposed in the original application.
3. The PNA antiviral activity needs to be examined at least in cell culture.

Reviewer 3:

It was a well-executed study that performed pretty much the intended tasks and led to high-quality publications, collaborations and preliminary data for funding. It was a good project with good significance.

## **ADDITIONAL COMMENTS**

Reviewer 1:

This research project seeks to develop a peptide nucleic acid based antiviral approach to inhibit hepatitis C virus replication. The rationale for the antiviral strategies is that PNA targeted to the RNA-RNA long-range kissing interactions should inhibit RNA-RNA interaction and stop virus replication. Hepatitis C virus is a major pathogen associated with the development of chronic liver disease, liver cirrhosis and hepatocellular carcinoma. Development of a novel antiviral approach to inhibit the virus should decrease the liver diseases associated with HCV. The PI is an expert in the PNA based antiviral approach for HCV and HIV. She has developed collaborations with outstanding investigators in the field. These are the strength of this research. On the other hand, the weaknesses of this project are as follows. The productivity was slow during the last three years of support. It is surprising that the PI is still working on the same specific aims even after receiving three years of funding. The PI did not show convincingly that this antiviral approach is feasible. The project is still in the preliminary stage. The usefulness of PNA in the treatment of HCV infection may not be pursued in humans, since the HCV treatment response using small molecule drugs shows great success. These deficiencies dampen the scientific merit of the grant application.

Development of an alternative antiviral strategy to inhibit HCV is important. There are a number of antiviral approaches for HCV that have been tried already including siRNA, microRNA-122, antisense oligonucleotides, and peptides. These molecular targets are highly specific, and they may inhibit HCV replication. One of the major problems with these approaches is that their delivery to the hepatocytes in the liver will be a major challenge. The PI has achieved the specific aims proposed originally. Most of the preliminary results are derived from *in vitro* gel electrophoresis experiments and have not been tested in a cell culture model. A lot more work needs to be done to show that this anti-viral approach is successful. The progress has been very slow.

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**Project Number:** 0863302  
**Project Title:** Impact of Parental Smoking Cessation and Residential Hazard Reduction on Pediatric Respiratory Health: A Pilot Investigation  
**Investigator:** Kabala, Stanley

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### ***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:

This project addressed the impact of parental smoking cessation and control of other sources of indoor air pollution (combustion fume and allergens) on the respiratory health of children. This is certainly a very important public health topic. The project itself addressed the interface between public health practice and public health research, building an evaluative research study into an existing service-delivery program (Healthy Home Resources, or HHR). The hypothesis was that enhanced educational outreach with parents who smoked cigarettes would improve living conditions, lead to an increase in knowledge, and lead to increased school attendance and decreased morbidity in children residing in these households.

The project ran into unforeseen logistical issues, namely the stoppage of the HHR in which this funded evaluation research was based; so the original stated objectives were partially met. After the shutdown of the HRR, alterations to the objectives were made through communications with the funding agency.

The original research design and methods seemed to be adequate in light of the project objectives, and it appears that the project began to be implemented according to that design; but the number of participants was smaller than planned, and there was limited follow-up capability. It is mentioned that 61 families were recruited, but data are presented only for 30 because that was the number that completed the initial baseline assessment. Was follow-up data for this special project ever collected? This was unclear and should be specified in the report, along with more precise detail about exactly what was and what was not accomplished.

The data were to be analyzed at Duquesne University, but the extent of the results presented was very superficial. The analyses presented were very cursory. Basing the strong inferences the investigators made on these analyses was not really warranted. The data were not delved into in enough detail to leave one feeling confident that appropriate inferences could be made, i.e., the data were not sufficiently analyzed to answer the research questions. It appears this research team is lacking in statistical data analysis expertise, which could potentially have also been achieved in collaboration with the University of Pittsburgh, Graduate School of Public Health.

Table 1 presents the distribution of expired carbon monoxide readings in children and their parent who smoked, symptoms, lost school days, use of rescue medication, and emergency room visits. Of course those exposed to secondhand cigarette smoke (SHS) are going to have much lower expired CO levels than active cigarette smokers, but a cross-tabulation of parent by child expired CO levels needs to be carried out. Also expired CO has a short half-life of just a few hours, so considering the time of day the reading was taken would be important. The statement is made that there was no correlation between parent expired CO level and health outcomes, but the actual smoking of parents and rules against smoking in the home and car need to be integrated into the data analysis in order to draw stronger conclusions.

An explanation was given for changes made to the research protocol. Considering the number of subjects relative to the target goal, the original target goal was to recruit n=50 participants, and n=30 were recruited. Under the circumstances, this achieved sample size does not seem unreasonable. There seemed to be no follow-up data after baseline: did parental smoking change over time? Was this associated with an impact on the health outcomes of their children? Apparently there were no longitudinal data collected for this pilot project, but this needs to be clarified along with many details to describe more precisely what data were and were not collected for this project.

Sufficient information was provided to support why the project did not meet its original objectives for recruitment. The number achieved seems reasonable under the circumstances of the HHR shutdown. The question is what happened to the longitudinal follow-up for the impact of smoking cessation?

The small amount of data presented and the lack of analyses of that data indicate that sufficient data and information were not provided to indicate what, if anything, could be learned from this project.

#### Reviewer 2:

The project's original stated objectives were: 1) to develop local, community-based partnerships between a non-profit community-based organization (CBO), a university, and the community; and, 2) to provide an educational outreach intervention to smoking parents and caregivers to promote smoking cessation and residential hazard awareness. The original design was a pre-post assessment of 50 families; however this design was abandoned when the CBO was defunded and forced into dissolution prior to completion of all of the pre-intervention assessments. The scope of work was then revised to include: 1) a literature review regarding in-home service delivery models for childhood asthma; 2) a meta-analysis to determine regionally (Pittsburgh) relevant exposures contributing to asthma incidence; and, 3) evaluation of the at home asthma education services previously provided by the CBO. The key difference between the proposed (unfinished) pilot and the revised project appears to have been the focus on smoking cessation in the original plan, which included CO monitoring before and after the intervention in both adults and children. The original design and methods were adequate, and baseline data were collected from 30 families. These data provide important and provocative information, but the small sample size precludes any true conclusions. (Though conclusions are drawn in the report, these cannot be assumed true, since the sample was too small to state that there were no correlations.)

With respect to progress on the revised aims, it is hard to assess. There really is no evidence of a systematic literature review or meta-analysis, though the discussion section of the final report addresses the questions that were posed. The analysis of regionally specific environmental triggers was unsuccessful due to geographic homogeneity of the sample. The evaluation of the CBO's effectiveness was thoughtfully done but lacked specificity regarding many important elements. Conclusions are presented without quantitative data (for example, "Participant families continued to employ the equipment...from the intervention;" and "there was clear evidence that parents had taken steps to reduce child exposure to tobacco smoke.") The cost-effectiveness conclusions are based on extreme assumptions, namely that out-of-pocket costs per family are \$2290 annually from age 9 to age 18. Overall, progress on meeting the revised aims must be considered "acceptable."

### Reviewer 3:

The project did not meet most of the stated objectives. Of note, the objectives changed greatly through the course of the project and included three distinct set of objectives proposed. The latter two sets of aims were not supported with study plan/methods descriptions or analysis approaches.

The first set of objectives outlined in the strategic plan (noted as "a" through "e" on page 13), was accompanied by a relatively well-described study plan for achieving the objectives and a poorly-developed analytical plan. Initial progress was accomplished for "a" and the beginnings of "b." Due to unexpected loss of funding by the partner community organization, the opportunity to conduct the project and aims was lost. This was explained adequately by the investigators and led to a new set of two revised aims in their SFY10 progress report (page 3). These aims were substantially different in that the conduct would not require primary data collection and interaction with community members but was anchored in activities that included review of existing data. Despite the completely different methodological approaches that would be required for these new aims, there were no additional methods or study plans to accompany these new aims. They were also vaguer than the initial set of aims, and the absence of accompanying methods/analysis plans made it difficult to be clear exactly what the planned outcome would look like.

One of the new aims suggested an opportunity to review and summarize the experience of the community organization's program with historically collected data. However, the investigators go on to note that after discovering the loss of the viability of their community organization partner, "the investigators determined that archival records for both the pilot and *AT HOME* projects had been destroyed." It is not clear why the investigator and the executive director of the organization who had planned to work on this together did not determine the feasibility of a data review before proposing such an aim. Again, no methods or analytical approach was provided to support the new aim. This aim was not accomplished due to the lack of feasibility.

The second of the new aims was not able to be conducted due to methodological flaws that would have been apparent if the methods had been proposed and developed along with the aims. Then in the final report a different and new set of three aims (page 11) is provided. One aim overlaps with the other two aims. Two of the new aims included a literature review. The review proposed has been well established in the recent published literature and would not represent a

unique or additional contribution. The reports did not demonstrate that a review was done. The other new aim was vaguely worded and came with no methodological approach description of an analytical plan. It is not clear how it links with any of the information provided in the final report.

In summary, the revised objectives were not met.

**Strength:** The original aims to leverage the community experience and connection of a community organization with the technical and analytical expertise of the university were well described and a valuable concept.

**Weaknesses:** After the initial plan fell through, subsequent aims do not appear to be well thought out. In future projects, the investigators should be sure to fully develop methodological and analytical plans that can support the aims. Vetting them with researchers or colleagues who have more experience with the methods and content would be helpful for setting the stage for success.

It is difficult to imagine that the initial aims with a sample size of 50 caregivers and children would be adequate to support the aims, and no power calculation of sample size information was provided. In the future, it would be advisable to work with colleagues who can help develop an analytical strategy and prepare a proposal with a defensible strategy.

The authors point out that the literature supports the inadequacy of using CO as a measure for tobacco smoke in their initial study. This should have been established before the investment was made to use this metric. In future related work, the investigators should become familiar with the rich literature on the use of cotinine measures in biological samples (hair, urine, saliva) for such purpose.

The data and information provided were not well linked to the evolving objectives. In the end, the final report is largely a description of the community organization's program, which was not the goal/purpose of the project, as well as much detail about the initial, no longer relevant original aims.

***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 potential significance of this project for improving health was strong. Parental smoking continues to pose a major public health problem to the parents who smoke as well as their children. Family-based interventions to address this problem are needed. However, as completed, the value of the research towards eventual improvement in health outcomes is minimal. This would not have been a high-impact study to start with, given the limited budget; but given the troubles encountered with the Healthy Home Resources shutdown and the cursory data analyses, the information generated by the study is indeed quite limited.

There were no major discoveries for prevention that are attributable to the completed research project, or evidence presented that the smoking cessation intervention had any impact at all. Because the data presented was so cursory, it was uncertain if there was any advance in knowledge on the impact the intervention had on parental smoking and its sequelae in children.

It was disappointing that there were no future plans for this research project, with no intent to apply for future funding. However, this was due in no small part to the fact that the community partner, Healthy Home Resources was shut down, which essentially precluded progress with the current project, let alone future projects.

Reviewer 2:

This is an extremely important area of focus, and the impacts of secondhand smoke and environmental exposures on childhood asthma require careful study. The proposed project represented a significant and timely innovation. However, the unfortunate circumstance of the CBO's closing did not allow these aims to be realized. The resulting knowledge from the revised work plan adds little to scientific knowledge in this field.

Reviewer 3:

There is no clear impact of this project on improving health. There were no products that will impact services, risk factor reduction, etc. The investigators note no future plans for this project.

Strengths: The concept (initial aims) was meritorious.

Weakness: The project failed to recover from the initial challenge of losing the community partner. Perhaps reaching out to some of the national organizations or investigators doing similar work might have provided some helpful suggestions on formulating successful alternative aims.

***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:

There was no leveraging of project funds. No leveraging of funds was expected that I could discern, so this was not an expectation. Graduate students (two master's students) did contribute time to the project, which would have enabled more work to be accomplished for the grant funding and contributed to their educational experience.

The researchers are not planning to apply for additional funding in the future to continue or expand the research, so the funding will not be leveraged to achieve future funding either.

Reviewer 2:

No additional funds were obtained or grants achieved.

Reviewer 3:

The project did not leverage additional funds or gain additional grant applications.

Weakness: On the contrary, attempts to find other support to carry forth the original aims were unsuccessful. The original project relied on leveraging a community organization that was not sustainable. While this was not under the control of the investigator and was unfortunate, the lesson learned may be to think about future projects that are not so dependent on a single partnership.

***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:

No licenses, patents, or commercial development opportunities would be expected from this project, and none materialized. This project could potentially have led to a nice peer-reviewed publication based on the novelty and the research strengths, but it does not appear that this is a possibility given the present state of the study and data analyses.

Reviewer 2:

There were no peer-reviewed publications or other projects.

Reviewer 3:

No peer-reviewed publications or commercial products were developed. The investigator notes no plans to submit publications.

Weakness: There were no outcomes from the project to support a publication or product.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

It is conceivable to view the partnership with the University of Pittsburgh School of Public Health as a step toward developing improvements in infrastructure due to guidance provided on ethical conduct of research, development of a survey instrument, and the use of statistical software. From the write-up, it is difficult to determine the extent of this interaction and if it led to any partnerships that will be sustained in the long term.

Dr. Tobin's role changed during the course of the project due to the shutdown of Healthy Home Resources, moving from an executive director to more of a PI role, which speaks to investigator roles changing to help carry out this research.

Funds were used to pay for effort on the project performed by two masters students; presumably these were graduate assistants McKee and Snedden at 2% effort each, clearly a very small amount. A greater percentage of effort was funded for paid interns McCalla and Duffy.

Reviewer 2:

There were graduate students involved in the project, and the collaboration between the university and the CBO appears to have been significant for the university.

Reviewer 3:

Strength: The relationship developed between the university and the community organization former executive director as a partner in research may be useful for future development of healthy housing community work at the grantee's 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:

A collaboration with the American Respiratory Alliance was arranged with the community for recruiting families, and a similar collaboration is mentioned with Children's Hospital of Pittsburgh. The University of Pittsburgh Center for Minority Health and Greater Pittsburgh Literacy Council were also mentioned as partners to work on ensuring that the project materials were at an appropriate educational level for the target audience. Tobacco-Free Allegheny was another partner for the smoking cessation intervention for parents who smoked. Thus, the plans for this study were to bring together an impressive array of community partners with complementary expertise.

Although new collaborations were formed to submit the proposal and implement the project, due to the loss of the community partner (Healthy Home Resources) it appears the researchers are not planning to begin any collaborations as a result of the research. The extent and depth of the collaboration with the University of Pittsburgh School of Public Health is not entirely clear from the write-up.

Reviewer 2:

The strongest feature of this project was the close collaboration between the university and the CBO. It is not clear whether any new collaborations will result.

Reviewer 3:

Weakness: The investigator does not identify any future plans for continuing healthy homes work similar to that proposed in this project or with the community partner former executive director.

Reviewer 3:

The project failed to meet the objectives. The project was unable to recover from the loss of the opportunity to complete the initial set of objectives. Some of the initial objectives were not well

thought out and vetted (e.g., use of CO as a metric for tobacco smoke exposure, statistical power). New revised specific aims were not well developed and failed from methodological flaws that could have been recognized before committing to aims that were not feasible.

## ***Section B. Recommendations***

### **SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

#### Reviewer 1:

1. With baseline data for the n=30 families that participated, these data need to be analyzed more rigorously with respect to parental smoking. The biomarker data are helpful but are limited by the short half-life of expired CO. Cross-tabulating the self-reported smoking data by the biomarker, cross-tabulating the parent-child expired CO by ordered categories that also included rules about smoking in the home and car would be helpful. If possible, integrating the secondhand smoke exposure data with exposure to other allergens in relation to the health outcomes would be a very good idea. There may be limitations in the technical expertise to carry out sophisticated analyses, but hopefully at least the cross-tabulations and thinking through the data in a more thorough fashion would be very helpful and not unreasonable to ask for, given the investment of resources to generate these data.
2. This write-up needs to be edited to clarify more precisely exactly what data were collected and when. The reviewer appreciates that the Healthy Home Resources shutdown had a major adverse impact on the project as planned, but the details with respect to what actually was accomplished and what the revised plan called for were not delineated in a clear and precise fashion. For the actual data related to the originally planned project, explain whether or not any longitudinal follow-up was collected for these n=30 families. If it was, it should be incorporated into the analyses described above even if the numbers are small.

#### Reviewer 2:

1. The literature review regarding in-home service delivery models for childhood asthma was sparse and could be more comprehensive and detailed.
2. The evaluation of the CBO's activities lacked detail and specificity and should include more quantitative data.
3. The conclusions drawn from the small pilot study are not substantiated.

Reviewer 3:

The project failed to meet the objectives. The project was unable to recover from the loss of the opportunity to complete the initial set of objectives. Some of the initial objectives were not well thought out and vetted (e.g., use of CO as a metric for tobacco smoke exposure, statistical power). New revised specific aims were not well developed and failed from methodological flaws that could have been recognized before committing to aims that were not feasible.

1. In future projects, the investigators should be sure to fully develop methodological and analytical plans that can support the aims and are clear to reviewers and others interested in their work. Vetting them with researchers or colleagues who have more experience with the methods and content would be helpful for setting the stage for success.
2. In future related work, the investigators should become familiar with the rich literature on the use of cotinine measures in biological samples (hair, urine, saliva) for such purpose.
3. Connecting with the multitude of national organizations, state level activities, or investigators doing similar healthy homes work might have provided some helpful suggestions on formulating successful alternative aims when faced with challenges.
4. Recognize the fragility of community organizations and develop a strategy that will enhance successful sustainability, perhaps by linking to more than a single organization and organizations that are not reliant on single, soft money funding sources.
5. Be clear about your statistical power or sample size needed if doing quantitative analyses.