

# **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 (1.73)

#### **Project Rating:**

<b>Project</b>	<b>Title</b>	<b>Average Score</b>
0862401	Methods and Strategies to Incorporate Radiotherapy Delivery Uncertainties in Clinical Trials Outcome Analysis	Outstanding (1.33)
0862402	Development and Analysis of an Infrastructure for Review of Modern Clinical Trials that Include Radiotherapy	Favorable (1.67)
0862403	Screening For Depression and Referral for Treatment of Cancer Patients	Favorable (2.00)
0862404	Assessment of Methods to Increase Latino Enrollment into Cancer Clinical Trials	Favorable (1.67)
0862407	Quantitative Imaging Biomarker Tools	Favorable (2.00)

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**Project Number:** 0862401  
**Project Title:** Methods and Strategies to Incorporate Radiotherapy Delivery Uncertainties in  
Clinical Trials Outcome Analysis  
**Investigator:** Xiao, Ying

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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 tasks of the project were: A) to quantify the uncertainties associated with radiation therapy delivery process with accumulated data, which include identification of key components of the process where potential variation can occur, uncertainties associated with each component and the accumulative effect from all; B) to research the optimal statistical methods for propagating these uncertainties in outcome analysis modeling; C) to implement these mathematical methods into established biological modeling open source software system with consideration for further extension and/or updating, and D) to develop a reverse process that can start from the endpoint of the outcome and predict the limit for uncertainties, thereby offer outcome based quality assurance guideline for the delivery technologies. Based on the progress report, it is my evaluation that these objectives have been met. The research design and the methods used were adequate. The results are nicely summarized and are in line with the original goals of the application objectives listed in the strategic research plan. The data were sufficiently developed to answer the research questions posed, and they were reported at national meetings as well as in peer-reviewed publications.

Weaknesses: None noted.

#### Reviewer 2:

The objective of the project was to systematically examine errors in radiation therapy delivery resulting from the vagaries of imaging during the treatment process. Through the clinical trial data submitted by investigators credentialing for RTOG protocols and submitted plans during the review process for patients being entered on trials, the authors examined the various sorts of errors that could theoretically affect outcome in terms of cancer control.

The authors achieved their stated goals well within the parameters laid out for the proposal. The data and information provided were well done and applicable to the project objectives initially proposed. They divided their proposal into tasks and have nicely laid out the results to define their questions and answers. The major strength achieved in this proposal was to design and implement a stronger multi-institutional QA system for image guided clinical trials in an effort to help decrease the variability in treatment delivery among institutions.

The only major weakness not acknowledged by the researchers is the variability of biological systems, i.e., tumor masses and their microscopic spread is not something that can be defined by physics, but leads to variability in treatment plans based on the experience of the treating physicians. It will be important to continue to allow some variability in treatment plans, IGRT analysis and not attempt to dogmatically apply mathematical criteria that do not take these factors into account. While only limited numbers of imaging data sets were reviewed, the complexity of the task will require ongoing fine tuning as technology advances.

Overall, the results are excellent and achieved the stated goals.

#### Reviewer 3:

The project did not meet its stated objectives. They made some progress in investigating variation in dose profiles in radiotherapy, but little progress was made in connecting these uncertainties to clinical trial outcomes, which was the main stated purpose of the project. The main results of the project included papers on the variations in planned dose profiles among institutions, variations in actual delivered dose to planned dose, uncertainties in delivered doses, and quality assurance in intensity modulated radiation therapy and image guided radiation therapy. The main attempt to apply these ideas to outcomes in clinical trials involved the use of a methodology that has been little used in clinical medicine. This so-called evidence theory derives from the Dempster-Shafer theory of belief. Standard methods of analysis in clinical medicine are frequentist, in which we evaluate relationships in comparison to a standard or previous evidence without assumptions about what is more likely to occur. Increasingly, Bayesian methods are used, though most often this is done with weak priors so as not to make conclusions from prior, possibly incorrect, opinions. Dempster-Shafer theory of belief is neither of these, and it seems unlikely to take a major place in evaluation of, for example, the relationship between dose uncertainties and clinical outcomes. The one example given, in Table 5 on Page 16, shows the problematic nature of this information fusing. At 20 Gy, the rate of pneumonitis is given in ranges 15%-35% at MSKCC, 8.9%-18% at Duke, 23%-39% at MD Anderson. The 'fused' range is 2.2%-40.7%, and it is hard to see what the value would be of an enormous range like this. We need much more information to do anything with this, and probably need something like a hierarchical logistic model

***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: The uncertainty of radiotherapy delivery to the target lesion is a key factor in treatment outcome, but is often overlooked in the outcome analysis. The discrepancies are particularly important in clinical trials involving radiation. It is therefore essential to understand and quantify the uncertainties associated with the individual process of the execution of the clinical trials and evaluate the impact of these uncertainties to the treatment efficacy and side effects. The stated future plans are to incorporate the research outcome from this project to the proposed NCI clinical trial network (NCTN) conduct and investigations.

Weaknesses: A minor weakness is that it is somewhat unclear from the report how the investigators will expand on the current results and how they will be integrated in large national trial networks.

Reviewer 2:

The main beneficial result from this project is to decrease errors within clinical trial conduct. As clinical trials fine tune treatment, the accuracy of treatment of the defined patients being treated decreases the uncertainties of the obtained results. It is important that uniformity between patients on trial be maintained and the central review function created from this proposal helps. Improvement in patient outcomes both in cancer treatment and toxicity is a long-term goal of clinical trials and as such, improvement of clinical trial conduct will contribute to this goal.

The future goal of the project is to continue to plan a major role in clinical trial design and conduct.

Reviewer 3:

The beneficial impact of this project is mostly technical within radiation oncology, and is certainly not negligible. However, it is not large either, nor in line with the impact suggested by the original proposal. Overall, this would be a moderate impact for the expenditure.

***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:

Strengths: The investigators have applied for a large grant from the NCI for the clinical trial network (NCTN) core. Funding is pending.

Weaknesses: None noted.

Reviewer 2:

The authors have applied for funding from other sources that have not yet been reviewed or granted. No other funds are reported to have been obtained.

If funded, the major proposal for an imaging core grant will be a major strength resulting from this proposal. It is not clear how much the present proposal added to the newly requested funds.

Reviewer 3:

There were no proposals funded, and two somewhat related proposals submitted, but apparently not (yet) funded. They do not seem to have a future program planned to follow up on these results.

***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:

Strengths: The investigators have been quite productive and published their results in 3 peer-reviewed publications in recognized specialty journals: 1 in the *Red Journal* (2011), 1 in the *Phys Med Biol* (2012) and 1 in the *Med Phys* (2013).

Weaknesses: None noted.

Reviewer 2:

The author reports multiple abstract presentations at national meetings and three publications have been either accepted or published in high-impact journals (the “Red Journal,” “Medical Physics”). They do not plan to publish any further data directly from this research.

No licenses, patents or commercial impact resulted from this project

Reviewer 3:

There were three peer-reviewed publications resulting from this, two of them in good journals. While this is less publication than might be expected for a four-year project period, the papers were solid contributions to the literature. Overall, this is moderate-to-low productivity for a project this size.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

Strengths: They trained one new investigator (post-doctoral fellow, Dr. Chen, salary support provided from this grant), built data sharing infrastructure and an expert network in related areas of computational science, analytical modeling and data mining.

Weaknesses: None noted.

Reviewer 2:

The authors state (Page 4, Item 15) that they have built a data sharing infrastructure and an expert network (presumably at other institutions) for data mining and computation. These areas are likely important for the individual efforts in the future but no obvious institutional infrastructure improvements are reported.

They report having supported a post-doc from this grant but no new faculty was added.

Reviewer 3:

Although they have cited the following: "We have trained new investigators; Built data sharing infrastructure; Built an expert network in related areas, of computational science, analytical modeling and data mining," it is not at all clear that any of these qualify as enhancements to the institution's capabilities. There was support of a post-doc, so that should count, but the other areas in this criterion were not really affected.

***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:

Strengths: The investigators report collaborations for data sharing, IT development and scientific investigations with several groups: Fudan (Shanghai, China), MAASTRO (The Netherlands) and Duke University (USA).

Weaknesses: It is not clear from the report how the methods will be implemented in the NCI clinical trial network (NCTN) and who the collaborators are.

Reviewer 2:

The authors report multiple new collaborations for data sharing including institutions from Duke University, China and Europe. No new patents, commercial developments or local Commonwealth-significant developments are reported although one could consider the clinical trial improvements could be a generalized benefit. There do not seem to be any collaborative efforts with Pennsylvania hospitals outside the home institution.

Given the initial stated objectives, this physics/imaging study achieved its goals with no obvious weaknesses. The goal of attempting to improve QA in imaging related issues for cancer therapy were achieved and the centralized QA system for multi-institutional trials has been enhanced.

Reviewer 3:

There was a modest level of collaboration as they report: "Collaborators on data sharing, IT development and scientific investigations, Fudan, Shanghai, China: MAASTRO, Netherlands; Duke University."

***Section C. Recommendations***

**SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

Reviewer 1:

The results are compelling and the methodology and new insights could be useful in NCTN trials (a grant application has been submitted for funding the Imaging Core), but it is not entirely clear from the application how this will be done.

Reviewer 2:

None.

Reviewer 3:

1. One weakness of this project was that the original objectives were somewhere between difficult and impossible to achieve, at least within the budget and the time period. The main accomplishments were not in clinical trials outcome assessment, but in quantification and investigation of uncertainties in radiotherapy. This is in itself valuable, and perhaps the proposal would have appeared more realistic if it focused on that area.
2. If one did want to model the impact of dose uncertainty in clinical trials, then much better data need to be utilized. We would need the planned dose, the actual dose (estimated) both to the tumor and to sensitive surrounding tissues (lung, heart, gut, bladder, etc., depending on the tumor), and then outcome data, both in tumor response and in adverse events. This is feasible with substantial advance planning and the cooperation of the trial organizers. This could be of great value.

**Generic Recommendations for the Institution**

Reviewer 2:

Support of the QA initiative from this proposal is a worthy proposition. I would like to see more evidence that local hospitals contribute patients and more interactions with the investigators.

Reviewer 3:

Either the efforts should be limited to specific radiation oncology/physics objectives, or the plans and resources need to be expanded significantly to address the impact on clinical outcomes.

**ADDITIONAL COMMENTS**

Reviewer 2:

This project has very few weaknesses since they have generally achieved what they proposed. It had little direct benefit to the Commonwealth aside from the fact one could consider improvements in clinical trial quality to be for the greater good.

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**Project Number:** 0862402  
**Project Title:** Development and Analysis of an Infrastructure for  
Review of Modern Clinical Trials that Include Radiotherapy  
**Investigator:** O'Meara, Elizabeth

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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: As new radiation therapy techniques are continuously improving, clinical trials conducted in cooperative groups require appropriate management and analysis of the information. The research funded through this grant was designed to investigate methods to improve information management capabilities and educational facilities for personnel involved in clinical trials as well as to improve data analysis tools available for radiation therapy dose distribution review. These goals were achieved. The applicant acquired several new systems and upgrades for the Radiation Therapy Core Laboratory. To streamline the review process, they created Image Guided Radiation Therapy (IGRT) instructional documents for each process. The study provided a feasible solution to the data sharing issues between institutions. Furthermore, they evaluated the system's abilities to support Phase II and III clinical trials, and developed an automated plan-quality evaluation program for multi-institutional clinical trials. Finally, they established a Computer Assisted Theragnostics (CAT) network at RTOG. Based on the information provided in the final progress report, these objectives have been met. The research design and the methods used were adequate. The results are summarized in detail and are in line with the original goals of the application objectives listed in the strategic research plan. The data were sufficiently developed to answer the research questions posed, and they were reported in a peer-reviewed publication.

Weaknesses: None noted.

##### Reviewer 2:

The components of the work as stated in the project strategic plan are:

- a) Purchase enhancements for existing case review equipment
- b) Purchase new equipment for clinical case review
- c) Finish and equip Core Laboratory at RTOG Headquarters for education and case review
- d) Create infrastructure for remote review of cases
- e) Develop education and training modules to prepare PIs for review of particular protocols
- f) Recommend new tools for clinical case review
- g) Gather and analyze data on the effectiveness of tools for case review

h) Publish findings on case review efficiency with improvement recommendations for case review tools

Reviewing the progress reports submitted, components a-c were completed successfully. Furthermore, component d was accomplished through the incorporation of remote viewing and review mechanisms into the equipment and software installed in the Core Laboratory. Component e was not addressed in the submitted progress reports, it is not clear whether this goal of creating specific training modules for project PIs was completed or abandoned, this must be viewed as a weakness of the project's performance. It is unclear how the investigators intended to accomplish component f, whether by identifying new tools that could be evaluated, or by evaluating the tools on hand for various situations and recommending specific approaches for each case review scenario. The former was certainly performed. The latter was done in part, although the investigators failed to adequately disseminate their findings to the community of radiation oncologists who could benefit. The investigators describe a multitude of studies performed to evaluate the various case review tools in a number of contexts as proposed in component g; this is viewed as a major strength of the project. There is concern that given the search space involved in this project, covering all possible case review tools and sites in which radiotherapy is applied, that the results obtained in the project appear anecdotal rather than definitive. However, this is to be expected given the number of permutations as described above, and this does not detract from the efforts of the investigators to evaluate specific case review situations. The project, however, exhibits a weakness in its limited publication record, failing to adequately accomplish component h.

Reviewer 3:

The objectives of this project are to examine the use of new tools acquired by RTOG as time-saving devices in the review of increasingly complicated clinical trials. The authors state that they plan to provide methodologies for management and metrics to demonstrate the increased efficiency by increased computer analysis.

**Strengths:** It seems the ACR purchased and installed multiple planning systems from various manufacturers to enable the analysis of data from most institutions using standard of care equipment. How much of the grant funds were used to obtain these systems is not clear.

The authors created an IGRT data integrity checklist to enhance the institutional credentialing process. They targeted several specific RTOG trials to compare automated plan review vs. manually assessing the submitted plans focusing on both accuracy and efficiency. Page 19 of the final report shows data confirming that the automated reviews are as accurate and take much less time to complete than manual reviews, but this seems to be a minor outcome of the proposal in contrast to the initial goals.

**Weakness:** It seems the stated goal of decreasing the time for review was a minor endpoint in the reported data. No statistics were kept to verify the significantly increased efficiency as had been stated in the initial proposal making publication somewhat difficult.

Overall, the study met its stated objectives and provides a significant step forward in improving the uniformity of subjects places on clinical trial.

*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: Novel treatment modalities are now routinely used in large Phase II and III clinical trials. The research funded through this grant is important because it will allow incorporation of these technologies in large multi-institutional clinical studies. The systems put together by the applicant may improve the efficiency of the review process while maintaining quality. This challenge is approached by: 1) identifying and implementing more efficient case review tools; 2) creating a case review environment that optimizes the use of existing equipment; and 3) improving remote review capabilities to allow for situations where it is not possible for one or more individuals to be involved in a central review process.

Weaknesses: None noted.

### Reviewer 2:

This project is definitely needed in order to streamline the execution of radiotherapy clinical trials while the technologies utilized in them become increasingly complex. Comparative radiotherapy trials between technologies have been a contentious topic and have raised concerns over the evidence justifying adoption of new technology. This has encouraged calls for proper clinical trials documenting the merits of novel radiotherapy methods. However, if these methods are not applied consistently across the required multicenter studies, the trials may not show a benefit even though the technique itself is useful when properly utilized. This highlights the need for efficient and effective case review methods such as those investigated here. This impact is a strength of the project. However, concerns over the extent to which the investigators have succeeded in defining standard case review mechanisms and disseminating these findings to the community exist based on the anecdotal progress reported by the investigators and the lack of publications stemming from this work.

### Reviewer 3:

The assessment of clinical trial treatment plans is important to be sure that trial objectives are met with as few deviations as possible. As part of this process, every clinical trial investigator must submit preliminary data to show that their system and understanding of the protocol requirements are reviewed centrally at the ACR for particularly complicated trials. The review of these plans can be extremely time-consuming. The main strength of the study that has been completed is to confirm that automated computer planning systems can achieve this more quickly and as accurately as a manual review.

The impact of this type of review is to improve our clinical trial quality by ensuring deviations from the protocol are minimized.

The study does not directly impact cancer control, prevention or outcomes.

The future plans for this project are not clear, but ongoing technological advancements make this an ongoing process.

Given that this is a QA project, I don't see any obvious weakness to their results.

***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:

Strengths: The investigators have applied for a large grant from the NCI for the clinical trial network (NCTN) core. Funding is pending.

Weaknesses: None noted.

#### Reviewer 2:

The CURE project generated data that has been included in two grant applications submitted to NIH. These applications have not yet been reviewed, as they were submitted in January 2013 after the end of the CURE grant on 12/31/2012. This is reasonable given the scheduled milestones and production of data for the CURE grant, and this is seen as an overall strength of this project. The investigators have no further plans to apply for additional funding based on the results obtained in this project, which is somewhat curious, although this concern is mitigated by the total amount of funding requested in the two pending NIH proposals (\$14,010,000).

#### Reviewer 3:

No new funding has been leveraged by these results, but two major grants have been submitted that have not been reviewed to date. The present project only indirectly adds to the validity of the submitted proposals.

***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:

Strengths: The investigators have been published their results so far in 1 peer-reviewed publication in the Red Journal (2011), and stated that several other publications are planned.

Weaknesses: None noted.

#### Reviewer 2:

A publication on the results of the comparative analysis of case review equipment with recommendations for tools was planned as part of this project. This is currently listed as intended for the future in the final progress report. The project generated one publication by Cui et al. on comparing multiple software packages to evaluate image registration, published in the

International Journal of Radiation Oncology Biology Physics in 2011. This is viewed as a component of the work supported in this project, but by no means the full report on the work supported or even the focus of the work. It is curious that the PI of this project is not a coauthor on this manuscript. It is seen as a weakness that the one publication generated by this project was submitted in March 2010, over 2.5 years prior to the conclusion of the period of support, and that no other work has been submitted since that time. This is an insufficient publication record, both in terms of number, quality, and relevance, for this project. Further publications on the findings of the investigators on the utility of plan review methods and recommendations for future clinical trials should be published as soon as possible.

Reviewer 3:

No future funding directly related to the results of this proposal is pending.

Only one peer-reviewed publication has resulted from this proposal in a high-impact journal (the "Red" Journal). The author reports at least one major meeting abstract was submitted and presented. The current proposal had formed a "part" of this sole publication along with other data.

As such, one weakness is the way the proposal had been written; it was more practical aiming to develop processes related to clinical trial QA rather than research (search for new knowledge).

No patents or licenses arose from this research.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

Strengths: There were numerous acquisitions of systems and upgrades that improved the Radiation Therapy Core Laboratory. The grantees trained 2 new investigators (post-doctoral fellows, Drs. Cui and Chen, each receiving 10% salary support from this grant). Thus, they have developed an infrastructure for review of modern clinical trials that include radiotherapy and have trained investigators to use these tools.

Weaknesses: None noted.

Reviewer 2:

The funds used in this project made major enhancements to the grantee's institution in a number of ways, and this is viewed as a major strength of the project. Much of the budget was used to purchase case review equipment and software, which will be an ongoing improvement to the ACR. Additionally, project funds were used to support a portion of the salary of two post-doctoral fellows in years 3 and 4 of the project.

Reviewer 3:

Weakness: The research did not result in any physical improvements/commercial products or direct community impact within the investigator's institution.

With respect to new trainees/education, the investigators report 2 post-docs were included in the project with no new faculty coming from out of state. Surprisingly, with no publications the role of the post-docs remains unclear to me.

***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:

Strengths: The investigators report collaborations for pilot studies of the systems with several groups: Fudan (Shanghai, China), MAASTRO (The Netherlands) and Duke University (USA).

Weaknesses: None noted.

Reviewer 2:

The project initiated collaborations in the review of clinical trials employing radiation therapy with researchers at Fudan in China, at MAASTRO in the Netherlands, and at Duke University in the United States. This is viewed as a major strength of the work.

Reviewer 3:

With respect to the stated goals of the research, that being improvements in clinical trial QA process, the investigators report new collaborative efforts internationally and within the United States. Given the nature of the research conducted, these collaborations are not unique to the funded project but seem to overlap with the basic RTOG goals. The direct impact for the Commonwealth is negligible but has a larger focus of improvement in the conduct of clinical trials nationally.

***Section C. Recommendations***

**SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

Reviewer 1:

None.

Reviewer 2:

1. The project has so far not published or disseminated its findings appropriately. This is a significant weakness given that the point of developing case review tools for radiotherapy trials is so that the community can benefit from them. The project needs to publish the variety of comparative case review studies it has performed so far.

2. The project's strategic plan described the generation of training modules for study PIs to prepare them for the case review process. These do not appear to have been created, and should be and should be disseminated as should the recommendations for case review procedures.

Reviewer 3:

While the investigators stated up front that the goal of the research which was to examine time and efficiency of submitted clinical trial cases, it would have certainly been of interest to document their efficiency rather than stating it was just obvious. Certainly, they could have compared process and software to assess this along with other parameters such as the time involved for the submitting physician to achieve a suitable plan and submit it. Efficiency should be extended to the design of the clinical trial radiation parameters to make trials easier to plan and submit. Some trials have radiation parameters that are very difficult to achieve at the time of planning and research such as this could help make accruals easier.

**ADDITIONAL COMMENTS**

Reviewer 3:

Based on the results reported, it seems the investigators achieved what they said they were proposing. The efficiency measure they reported, i.e., time to review cases, was only a very tiny part of what was done. Nonetheless, they achieved the practical goal of the proposal, which was to improve efficiency of complex radiation plans submitted to the ATC.

There is little direct impact on the home institution but one could generalize the benefit of higher quality clinical trials benefitting patients nationwide. The study has no direct effect on cancer control, prevention or treatment.

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**Project Number:** 0862403  
**Project Title:** Screening For Depression and Referral for Treatment of Cancer Patients  
**Investigator:** Watkins-Bruner, Deborah

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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:

The project tackles pertinent and timely questions regarding detection and treatment of depression in cancer populations. Recruitment goals were achieved in a 37-site study even with barriers of IRB-requested changes and PI change. Changes to design incorporated pertinent and timely questions (e.g., effectiveness of distress thermometer, diagnostic interview for multiple depressive disorders, protocol for positive suicidal ideation screens). Baseline design and methods were followed as proposed, with the exception of clinical interviews, which are not reported. Follow-up design and methods may not have been completed or followed, as they are not reported.

Baseline data is supplied only for description of sample and institutions, with limited information related to the specific aims. Utilized cut-off scores should be reported with evidence-based rationale. Subsequently, the baseline rates of positive screens per screening instrument should be reported (HSCL, PHQ9, PHQ2). The number of baseline clinical interviews (SCIDs) completed should also be reported with calculations for sensitivity, specificity, positive predictive values, and negative predictive values per primary screening instrument, as baseline data is reported as complete in 3/2011. Without this information, the reviewer is unable to assess the outcome, impact, and effectiveness of the project according to specific aims.

Three-month follow-up data is also not reported, but if completed should yield an assessment of effectiveness of screening and referral system. What percent of participants experienced improved symptom burden?

##### Reviewer 2:

**Strengths:** This project met the stated objectives and adhered to the research method proposed. The project aimed to document (a) rates of patients who screened positive on major depression via a self-reported questionnaire and structured telephone interview, (b) proportion who were not receiving proper treatment to deal with the depression, and (c) reassessed proportion who were not receiving proper treatment to deal with the depression three months later. These aims were achieved by enrolling the targeted number of participants.

Standardized and relevant scales (the *PHQ-9* and the *HSCL-25*) in the questionnaire and clinically relevant tools (the *Structured Clinical Interview for Diagnosis- DSM-IV* and the *Assessment of Mental Health Services and Barriers to Care*) in the telephone screening session were used.

Thirty-seven institutions participated, including 2 full and affiliate institutions and 35 Community Clinical Oncology Program (CCOP) member and component institutions.

Weaknesses: Aim 3 was to provide referrals for treatment to those depressed persons not already in treatment and follow up with them three months later to determine whether they had completed the referral and experienced an improvement. Barriers to care were to be assessed during the 3-month follow-up, yet no actions were taken or even suggestions made for future study of how to overcome such barriers. Whether or not patients reported decreased depressive symptoms at three-month follow-up as a result of utilizing the referred resources was not reported. This is a major omission in executing this project, as untreated depression has a significant impact on patients' recovery from cancer and quality of life in general.

It is well known that depression per se and utilization of the health care system is closely related to the socio-economic status of patients; yet, this project did not address or consider such an influence. Similarly, variation in prevalence of depression or major depression among cancer patients can be attributed to different phases of survivorship, type and stage (severity) of cancer diagnosed, premorbid condition of depression and other psychiatric conditions, not solely to variations in definition and measurement of depression, as the investigators implied. Omission of these factors in the current project's investigation limits validity of the results and evidences lack of scientific rigor.

As the investigators reported, most study sites (78%) routinely screened for distress at their radiation facility; mental health services were most widely available in general medical facilities (88%) at a per service cost (72%) to patients. No information was provided as to whether such high-quality service had been established before this project began or has been improved as a result, even in part, of executing the study protocol.

No professional presentation or publications were generated from this project (although four publications were reported from other projects). Current reports are far short to be incorporated to meet their stated ultimate goal of this project, which was to design and evaluate an intervention involving a depression care specialist.

### Reviewer 3:

This project, when it was originally approved, had important primary and secondary objectives. The study's original design methods were, however, flawed and problematic. There were a number of methodologic issues regarding the assessment and management of patients with psychosocial distress and suicidal ideation. In addition, the study chair stepped down. The IRBs at several of the sites would not allow the original project to continue due to, or related to, the above problems and so the original project was closed on July 14, 2009.

A new study chair, Dr. Lynne Wagner from Northwestern University in Chicago, Ill., was appointed by the Radiation Therapy and Oncology Group and substantial revisions were made to

the project. The primary objectives remained, but the secondary objectives were substantially revised. Changes were made to the screening tools used and much less emphasis was placed on the barriers to care. The emphasis of the project shifted towards asking questions about the psychosocial services provided at the sites and institutions in the study. The original study had interesting questions as its objectives but they could not have been answered with the original design. The substantially revised project was more modest in its objectives, used other instruments that are more clinically useful such as the NCCN Distress Thermometer, and tried to assess the level of psychosocial services in radiation oncology sites, a more modest but nevertheless useful objective.

The original study had patients who were identified with major depression but who waited for up to two weeks to speak with trained interviewers, which was clearly a problematic lag time for patients with hopelessness or suicidal ideation, intent or plan. This major design flaw was corrected in the revised study with patients given treatment options and resources in a more timely manner, and which was approved by the IRB sites.

Four hundred patients were originally targeted to be in the study but 454 were enrolled. Since the study was substantially modified, and it doesn't appear to have a control group, it is difficult to understand what the measures will be for statistical significance. The patients in the study turned out to be mostly female, white patients with early breast cancer.

**Strengths:** The strengths of the project were that sites were evaluated for availability of psychosocial services. In addition, cancer patients who were receiving radiation therapy were evaluated using several measures of depression and psychosocial distress. In addition, there were quite a few sites in the study, showing an interest in the topic of screening for psychosocial distress.

**Weaknesses:** The original objectives of the study concerning barriers to care were not able to be evaluated in the study because of the flaws in the study design. In addition, there was a predominance of female Caucasian patients with early breast cancer. It is unclear if this was a targeted patient population for this study and if the numbers of other types of patients are enough to achieve some statistical significance when the data are finally analyzed.

***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 data are incomplete. This study does provide evidence for feasibility of screening for depression in terms of patient and multi-institution participation. This study does not yet provide evidence of impact or effectiveness of the tested screening instruments' ability to detect depression, nor the telephone assessment and referral system to connect patients to effective treatment. Investigators do not indicate if this data was collected or completed. If completed as proposed, this study promises to yield data about effectiveness of screening measures compared to gold-standard diagnostics. With incomplete data, future plans are also not delineated.

Reviewer 2:

**Strengths:** This project described the prevalence of major depression among cancer patients undergoing radiation therapy using several convenience samples.

**Weaknesses:** A list of mental health resources was given to patients who were identified as having major depression, yet whether the patients benefited from the resource by improving their depressive symptoms was not examined.

Other than printing and mailing the list of mental health resources, it appears all the study budget was spent for study personnel, not for patient care.

An application for more ambitious, federally funded (National Cancer Institute) project evaluating means of addressing barriers to care and improving the completion of referrals and the assurance of effective treatment for depression was proposed; yet, the likelihood that results from the current project could be used as sound preliminary data is slim.

Reviewer 3:

The study used several screening tools for depression in cancer patients in the setting of radiation oncology treatment, in 37 institutions. It was found that most of the sites routinely screened for distress at their radiation facility. They also found that mental health services were more widely available in the general medical facility than in the radiation facility and that patients were most frequently charged for the service. This information might be helpful if an institution was interested in a different model of providing mental health services for its patients with cancer who were being treated for radiation. It does not appear that information about patients' insurance was collected prospectively in this study so it is difficult to know what the issues were regarding fee for service and how many patients were unable to receive care (a possible barrier to care). The patients were mostly female, white and with early breast cancer, but without a control group it is hard to extrapolate what this means for improving health care. The authors note that they are planning on submitting articles to peer-reviewed publications. There was no change in outcome, impact and effectiveness attributable to this project. There were no major discoveries, no drugs or new approaches for prevention, diagnosis and treatment. There were no patents awarded. The authors note that they will apply for a more ambitious federally-funded project evaluating barriers to care but this aspect of barriers to care was modified from the original grant and was not really addressed much in the current project that we are now reviewing.

**Strengths:** The strength of this project is that there are now data received on psychosocial services in 37 radiation therapy sites and institutions.

**Weaknesses:** It is not clear if this data is robust or sufficient enough to provide a meaningful understanding of what might be useful, given the screens that were used for psychosocial distress, and the types of patients screened (women, Caucasian, early breast cancer were the main group of patients). The objectives of the study did not focus on this type of group.

***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:

Center resources were referenced as supporting. Plans were reported to pursue NCI funding for larger, subsequent study. However, data are incomplete for this foundational study per this report.

Reviewer 2:

Strengths: None

Weaknesses: Other funds supported this project (CCOP grant U10 CA37422 RTOG grant U10 CA21661).

Reviewer 3:

This project did not leverage any additional funds. The researchers note that they would apply for additional funding for a more ambitious, federally funded (National Cancer Institute) project regarding evaluating barriers to care. While the original project with its original objectives was focused on barriers to care, I am not sure that the replacement project is focusing on barriers to care, so much as screening for psychosocial distress. It is not clear whether the reconfigured project provides enough pilot data since the design was drastically modified, especially the section regarding access and barriers to care. We will need to wait for the final data compilation from the researchers and see what papers are published to see what data actually was collated and compiled, with statistical significance.

Strengths: The researchers note that they are going to apply for federal funding.

Weaknesses: No peer reviewed publications with the pilot data have been published so we do not know if there is enough good data here, with its greatly modified design, to obtain federal funding.

***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:

They reported plans to submit abstract for presentation and then a manuscript submission to peer-reviewed journal. The rationale for the delay in reporting baseline and follow-up data according to specific aims is not provided.

Reviewer 2:

Strengths: None

Weaknesses: No peer-reviewed publication or conference presentations were generated from this project.

Reviewer 3:

The project did not result yet in any peer-reviewed publications. The project did not result in any licenses, patents or commercial development opportunities. It does not seem that licenses, patents or commercial development opportunities were expected.

The authors note that they expect to submit articles to peer-reviewed publications.

Strengths: The authors note that they expect to submit articles to peer-reviewed publications. They were able to recruit patients, above the expected number, to the study. They did obtain data and did provide the data in their final report.

Weaknesses: As of this time, no peer-reviewed publications have been published.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

The diagnostic interview process was cited as a developed resource, yet data yielded by this resource is not reported. There were no new investigators. Two post-doctoral fellows gained experience in multi-site clinical trials.

Reviewer 2:

Strengths: The grant provided resources to the investigators for telephone depression screenings.

The study provided an opportunity for two post-doctoral fellows to be trained in national clinical trials research.

Weaknesses: The two post-doctoral fellows supported from this grant seem not to have generated anything from this project.

Reviewer 3:

The authors note that the resources permitted the opportunity for two post-doctoral fellows to be trained in national clinical trials research, adding future capacity for this work as a benefit. While this wasn't a training grant per se, and training and education was not explicitly noted in the objectives, indeed two post-doctoral fellows were trained.

Part of the funds were used for Dr. Wagner who was recruited from Northwestern University to oversee the project when the original study was stopped and a new PI needed to be found.

Strengths: The infrastructure was improved by training two post-doctoral fellows who are now able to be involved in future similar projects, especially if the researchers apply for federal funds.

Weaknesses: Other than the training the two post-doctoral fellows, there doesn't seem to have been more building of an infrastructure in the host institution at the University of Pennsylvania. Since the design and structure of the project had been considerably modified, and the new study chair was from Northwestern University, this issue is understandable given the significant changes that occurred in the project, almost from the beginning.

***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 developed with Dr. Wagner. Thirty-seven sites were included in this study with unclear geographic distribution.

#### Reviewer 2:

Strengths: Thirty-seven institutions participated, including 2 full and affiliate institutions and 35 Community Clinical Oncology Program (CCOP) member and component institutions. Collaboration with Dr. Lynn Wagner, Ph.D., psychologist, Northwestern University, Illinois, was established.

Weaknesses: None

#### Reviewer 3:

The project led to Dr. Lynn Wagner, Ph.D. from Northwestern University, collaborating as PI of the study. The research did not lead to new involvement with the community. The project was leveraged with an ongoing CCOP grant U 10 CA 37422 RTOG grant U 10 CA 21661. As such, 37 institutions participated and 35 community Clinical Oncology program members.

It was not noted how many of institutions or community groups were in the region or the Commonwealth. It was not noted as to the extent of collaboration envisioned by the authors, specifically as it related to collaboration in the region or Commonwealth.

Strengths: The strength is that the PI of the project was from Northwestern University. There were also 37 institutions and 35 community Clinical Oncology Program members.

Weaknesses: I am not sure where these institutions and community members were from, and not sure how many or if any of these institutions and community members were from the region or Commonwealth.

## *Section C. Recommendations*

### **SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

#### Reviewer 1:

1. Utilized cut-off scores should be reported for each screening instrument with evidence-based rationale. Which score was used for referral to diagnostic interview?
2. The number of baseline clinical interviews (SCIDs) attempted and completed should also be reported with calculations for sensitivity, specificity, positive predictive values, and negative predictive values per the primary screening instrument. The prevalence of each depressive disorder should be reported. The additional screening instruments should also be examined in association to diagnoses, given they are most commonly used instruments (PHQ9, PHQ2, distress thermometer). How much incremental validity is estimated by longer instruments? How does incremental validity compare to resource utilization per instrument? How many patients were already receiving treatment?
3. The number of follow-up interviews attempted and completed should be reported at proposed 3-month time point. The percentages of patients that experienced increased, decreased and stable depressive symptoms should be reported along with specific evidence-based criteria (e.g., change score, number of points) that signifies clinically significant change.
4. An opportunity exists with this study to describe the investigator team's handling of IRB concerns leading to development of a protocol to protect suicidal patients. What protocol was accepted by all IRBs? How many patients endorsed suicidal ideation? Number of actual suicides and lost to follow-up?

#### Reviewer 2:

1. Beyond documenting prevalence of depression in cancer patients using convenience samples, strategies to reduce the prevalence of untreated depressed cancer patients should be developed.
2. The study samples were extremely homogeneous in ethnic and SES compositions.
3. Impact of expected results was low. More scientifically rigorous research questions and study designs should be employed.

#### Reviewer 3:

1. The objectives need to be better linked the study group. For example, if the objective was to focus on women with early breast cancer, then that should have been part of the objective.
2. One of the weaknesses is that the large number of patients was female, Caucasian. It doesn't seem to have been enough of a heterogeneous group of cancer patients. It would be helpful for the researchers to review this and make sure that their subjects represent the diversity of people with cancer.

3. The authors note that they were interested in barriers to care. This might have been a vestige of the first set of objectives with the original design. It would be important, if the researchers are interested in barriers of care, to set the design in a more effective manner.
4. It would be helpful to understand the statistics and determine if this study was powered appropriately, and whether a control group is needed.
5. In order to not have the IRBs turn down the project, it would be helpful for a clinician who has expertise in clinical issues, to review the protocol and make sure that patients with significant clinical problems such as major depression, hopelessness and suicidality, are seen in a timely manner and provided with care. Sometimes waiting room studies are workable, but sometimes they are not, and it would be helpful to understand these issues so that study design doesn't have to be so drastically modified.

### **Generic Recommendations for the Institution**

#### Reviewer 1:

Data should be reported by each aim, including rationale for any incomplete data. There is much opportunity in this study to disseminate to impact national efforts to improve detection and treatment of depressive symptoms among cancer patients, and other populations.

#### Reviewer 3:

The original design of the project was quite flawed. It might be useful for ACR to consider having someone on the grant selection committee who understands clinical research so as to hopefully avoid very flawed designs.

### **ADDITIONAL COMMENTS**

#### Reviewer 2:

- A follow-up plan for depressed patients who were not utilizing proper services is recommended.
- Consider acknowledging and examining psychosocial factors that are closely related to depression.
- Scientific publications and presentations are recommended.

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**Project Number:** 0862404  
**Project Title:** Assessment of Methods to Increase Latino Enrollment into  
Cancer Clinical Trials  
**Investigator:** Watkins-Bruner, Deborah

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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 had 3 specific aims: 1) To develop and evaluate evidence-based, culturally and linguistically appropriate education and awareness programs and recruitment materials to increase enrollment of Latinos into cancer clinical trials, 2) To develop a Latino Cultural Competency and Recruitment Training Program for physician investigators and 3) To conduct a gap analysis of current RTOG sites with high density Latino populations and areas with high density populations and no RTOG sites. This project met all of the originally-stated specific aims. In addition, the original aims were expanded during the middle of the project to include African-American populations. These changes were approved in 2011.

Although all aims were met, one small weakness for Specific Aim 2 was noted: the original sample size of 100 was not reached and only 67 participants took part in the training.

The data provided in the final progress report are adequate and provide good evidence of the effectiveness of the study. In addition, additional data specifically for Specific Aim 2 (which I would have been very interested in seeing) are forthcoming – these data include the pre- and post-training minority recruitment statistics. One comment/question about these data is: Why did the researchers include American Indian/Alaskan Native in their numbers, given that the focus was on Latino and African-American populations?

Strength: The video of the cultural training program has been posted on the RTOG website which allows all RTOG members to use it.

Strength: Inclusion of both Latino and African-American populations.

All data and information provided in the final report were applicable to the project specific aims listed in the strategic research plan.

##### Reviewer 2:

This project had 3 major research objectives. The first objective was to develop programs and materials for enrolling patients in RTOG trials. Although the program and materials are poorly

described in the reports reviewed, it appears to have been reasonably well-constructed and applicable to a limited number of people. The second aim was to provide cultural training to RTOG investigators and staff. Again, although difficult to evaluate because of the lack of detail, this was done. The investigators do not provide detail concerning which clinical trials were selected for targeting. The number of people who were used to evaluate the training was small. The third objective was to use GIS models to assess the overlap of RTOG clinical sites with population centers where minority individuals resided. This was accomplished, although the analysis was somewhat obscure.

The research design appears reasonable but again sample size for training was disappointing. The investigators added African-Americans to the design and this was an excellent addition. Overall, the project had very important goals and the preliminary data generated, while inadequate to provide insight sufficient to take action, is likely adequate for additional applications for continued funding.

#### Reviewer 3:

The goal of this project was to develop and evaluate evidence-based, culturally and linguistically appropriate patient education materials and investigator training programs to increase the enrollment of Latinos in RTOG clinical trials in Pennsylvania and nationally. Additionally, cartographic modeling techniques were used to perform a gap analysis to identify disparities between current RTOG sites and Latino population density. During the grant period, the original focus on Latinos was expanded to include African-Americans.

The project successfully met its objectives of developing patient education materials and investigator training programs and using cartographic modeling to perform a gap analysis. However, the primary objective of increasing Latino (and African-American) recruitment by 10% has yet to be assessed. The investigators planned to target 4 protocols to assess the impact of the educational materials and investigator training program. However, no list of the targeted protocols was provided. Thus, it is difficult to assess the impact of the grant in improving accrual.

It also is unclear how the maps obtained using cartographic modeling will be used by RTOG to add sites with higher density Latino and African-American populations. A discussion of how the results will be used in the future would be helpful.

***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:

If the minority recruitment rates indicate an increase of minority participants in clinical trials, the impact of this project would be very significant. Current statistics indicate that minority individuals are recruited at a lower rate than white individuals into clinical trials. In order to assess the effectiveness of the trials, more minorities need to be included. If/when this happens, it can lead directly to better health outcomes for minority individuals.

No new discoveries, new drugs, etc., can be attributable to this project. However, the new cultural training program for physicians that was developed in this study can be considered a new and valuable contribution.

The researchers intend to apply for additional funding for the cultural competency training in 2013. I am assuming this funding will be used to disseminate the training.

Strength: The cultural training developed in this study can have significant impact on the health of minority populations.

Reviewer 2:

The benefit that would accrue from successful completion of this project is very significant. Minority recruitment into clinical trials is a very important and understudied issue. I believe that this project, while falling short of what might eventually be accomplished, has begun a critically important area of research.

The future plans as laid out in the summary (grant funding from PCORI) are on target and will, one hopes, be successful.

Reviewer 3:

This project has very high potential for improving the access of Latinos and African-Americans to clinical trials. As of yet, however, it is unclear how much impact the grant has had. The information provided by the cartographic modeling is interesting, but it is unclear how it will be used by RTOG to improve Latino and African-American recruitment into clinical trials.

The future plans for the research project are to submit a PCORI grant on cultural competency training. Also, a manuscript describing the impact of the investigator training program on knowledge, attitudes and changes in minority accrual will be prepared.

***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:

At the time of the final report submission, no additional funds had been received but the investigators did indicate that they would be submitting a future grant.

Reviewer 2:

Leveraging of the RTOG was accomplished as planned. The plans for future funding, as noted above, are excellent.

Reviewer 3:

No additional funds were leveraged for the grant activities. The investigators plan to submit a PCORI grant on cultural competency training.

***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:

Study results were presented at a professional conference, but no peer-reviewed publications were identified. However, the investigators did indicate identify three different publications for submission.

Small weakness: Given that this study started in 2009, it would be fair to expect to have seen at least one publication accepted or in press.

Reviewer 2:

The project resulted in two abstracts, but no publications in journals. They have plans for publication.

The plans are reasonable and in line with expectations.

Reviewer 3:

Two abstracts were presented based on the study findings. Three manuscripts are in preparation. The first will address the impact of the investigator training program on knowledge, attitudes and change in minority accrual pre- and post-training (the primary study endpoints). The second will be on validation of the Cultural Competency Assessment Tool. The third will assess mapping of clinical trials accrual.

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

***STRENGTHS AND WEAKNESSES***

Reviewer 1:

No improvements were made to infrastructure at the grantee's institution.

No new investigators were added.

Funds were used to pay for 1 pre-doc fellow. In addition, some funding was used to pay 1 undergraduate student.

Strength: Some grant funding was used to fund students.

Reviewer 2:

One student (pre-doc) was involved. No infrastructure improvements were made, although the tools developed could be counted as potential “infrastructure” development.

Reviewer 3:

There were no improvements to the infrastructure or new investigators added as part of this research. One undergraduate and one pre-doctoral student were supported by the grant.

***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 researchers collaborated with 2 companies from Pennsylvania to assist with the development and implementation of the cultural training.

Reviewer 2:

Minimal additional collaboration was realized.

Reviewer 3:

Two companies from Pennsylvania were funded to assist with the development and implementation of the cultural diversity training.

***Section C. Recommendations***

**SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

Reviewer 1:

I really enjoyed reading about this study. One recommendation is that the investigators provide the cultural training and the assessment tool to all researchers and practitioners and not limit access to members of RTOG.

Reviewer 2:

1. The sample size was inadequate to allow for definitive interpretation of the data. More people need to be included going forward.
2. The types of trials appropriate for these tools should be discussed. Going forward this needs to at least be considered.
3. The materials developed through this research study should be provided for assessment.

Reviewer 3:

1. The project successfully met its objectives of developing patient education materials and investigator training programs and using cartographic modeling to perform a gap analysis. However, the primary objective of increasing Latino (and African-American) recruitment by 10% has yet to be assessed. I encourage the investigators to complete these analyses as they will provide a test of the effectiveness of the Latino and African-American Cultural Competency and Recruitment Training Program.

2. The investigators planned to target 4 protocols to assess the impact of the educational materials and investigator training program. However, no list of the targeted protocols was provided. Such a list would provide more detail as to the disease sites that the investigators feel are more amenable to improvement in Latino and African-American recruitment.
3. It is unclear how the maps obtained using cartographic modeling will be used by RTOG to add sites with higher density Latino and African-American populations. A discussion of how the results will be used in the future would be helpful.
4. A statistical weakness is that the investigators state that they used a Wilcoxon-Mann-Whitney test to assess cultural diversity knowledge and attitudes of participants in the face-to-face RTOG training. This test assumes two independent samples. Since 42 of the participants completed surveys at baseline and follow-up, a more appropriate test is the Wilcoxon Rank-Sum test.

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**Project Number:** 0862407  
**Project Title:** Quantitative Imaging Biomarker Tools  
**Investigator:** Schnall, Mitchell

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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:

There were three stated objectives to this project: 1) analyze and refine tools to determine if enabling automated extraction of quantitative imaging biomarkers will improve the efficiency of the analysis of imaging data; 2) to develop a standards-based software platform to unify quantitative imaging tools for efficient image evaluation and data interoperability; and 3) to assess the platform in a study requiring evaluation of quantitative imaging data. The project met its objective by focusing on extending capability and functionality on one device (ePAD), and developing tumor assessment template for RECIST (hence reducing its original scope).

The investigators conducted an inventory of the tools used in the ACRIN laboratory in order to expand the functionality of these tools to integrate imaging outputs. However, this was not accomplished for all tools due to fundamental structure differences in analytical output and capturing descriptive language presentations. This was an ambitious task to accomplish given that most of the software applications do not provide open programming interface. Given this limitation, the investigators scaled back and focused on expanding the functionality of the tool they previously developed (ePAD) and developed a tumor assessment template based on the RECIST criteria.

The combination of the tool and the application platform ePAD-RECIST tool provides integrated workflow and summarize in a tabular form the quantitative measurements across time and also allow access to each lesion type and time points. The investigators evaluated the impact of this tool on the efficiency of the reader evaluation using the time matrix (time spent on reading the images). Given the amount of energy and time spent on this project and the seemingly efficient way of integrating and displaying the different outcome, the amount of time saved is very small (average less than 1 minute). It may be that reading time might not be the right matrix to measure the impact of the new tool. I am assuming the standardization, the visual display of all images taken serially, the prompt to look for lesion in subsequent images if observed at baseline, etc., will improve the reliability and quality of the data and reduce error. I don't think these attributes are captured in the assessment using the time matrix.

In the absence of such evaluation it is hard to say how much impact this tool will have in helping cancer researchers to make a clinical decision. In other words, the added value of this tool is not demonstrated quantitatively.

Reviewer 2:

According to the final report, “The purpose of this study is to evaluate, develop, unify, and evaluate standards-based tools that are used to collect, record, and analyze quantitative imaging data in order to discover imaging biomarkers for more accurate analysis of image results collected in clinical trials.” For the Aim 1 and 2, because of the differences in the fundamental structure of current available tools, the grantee made a necessary change to the original study design and performed study in concert with extending the functionality of the web-based electronic physician annotation device (ePAD). They further focused on testing and refining the image annotation database and data output of the ePAD RECIST Template. In the Aim 3, they undertook a formal reader study to assess the impact of using the ePAD tool on the efficiency of reader evaluation of quantitative imaging studies. Overall, the progress of the project is acceptable, and the technique developed in this project may help to improve overall reader time for data analysis.

Reviewer 3:

**Strengths:** The objective of this project was to develop and unify standards-based tools for collecting, recording, and analyzing quantitative imaging data for discovering and using imaging biomarkers for more accurate analysis of image results collected in clinical trials. The overall hypothesis was that by unifying the currently fragmented set of tools for quantitative image analysis, the evaluation process will be more efficient and accurate. The ultimate goal was to facilitate assessment of treatment response and clinical decision-making in cancer. Based on the evaluation of the progress report, I think that these objectives have been largely met. The grantees identified which ACRIN tools provided open programming interfaces and performed a detailed gap analysis, provided as an appendix. They also developed a web-based platform to store all image data according to NCI’s cancer Biomedical Informatics Grid (caBIG) Annotation and Image Markup (AIM) standards, and set up and tested project-specific DICOM servers populated with test cases. Together with the Stanford University team, the ACRIN installed and tested ePAD with the DICOM servers at ACRIN and successfully configured it to interface with both the ClearCanvas and dcm4chee servers. The grantees focused on improving the efficiency and analysis of RECIST assessments. A code was written to support unambiguous identification of target lesions and automated tracking (matching) of images across various time points, and a Reader Study Instruction Manual was created (also provided as an appendix to the final progress report). Finally, they undertook a formal reader study to assess the impact of using the ePAD tool on the efficiency of reader evaluation of quantitative imaging studies. This included a review of the RECIST 1.1 criteria and review of two test patient image sets as test cases using the ePAD RECIST tool to familiarize the reviewers with the RECIST template workflow and ePad software mechanics. The research design and the methods used were adequate. The results are summarized in detail and are in line with the original objectives and aims as listed in the strategic research plan. Conceptually, the approach was sound and should lead to improvement of the current assessment of imaging biomarkers.

**Weaknesses:** Not all data were sufficiently developed to answer the research questions. In the analysis of the reading time, the data does not support the conclusion that the method is efficient. This may be due to one reader’s bias, as stated. It is also clearly due to the limited amount of data.

***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:

I think by standardizing and integrating the imaging output, the tool developed here might have some beneficial impact for the cancer clinician. However, it is not clear if the added value of this tool on the existing practice is substantial.

Reviewer 2:

The beneficial impact of this project is moderate. The ePAD RECIST tool studied in this project may help to improve overall reader time for data analysis. This finding could have direct impact to the current clinical practice of using CT for cancer diagnosis. Since the reader D is an outlier in the study of Aim 3, it would be better to include more readers to validate their findings in future studies. Moreover, testing the software for PET/CT data or MRI images is desirable in the future plans.

Reviewer 3:

**Strengths:** The ultimate goal is to develop tools to facilitate assessment of treatment response and clinical decision-making in cancer. These unified tools will enable cancer researchers to validate and standardize methodologies and to share imaging data and related imaging meta-data for quantitative measurements of responses to cancer therapies. Thus, this work might enable oncologists to make better treatment choices for cancer patients.

**Weaknesses:** The benefit is not clear yet, given the scarcity of analyzed data.

***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 additional funding sought during this project period; however, the PI and one of the co-investigator are applying in response to an RFA issued by NCI.

Reviewer 2:

The project did not leverage additional funds. The grantee is planning to apply for additional funding in the future to expand the research. Specifically, Dr. Rosen has applied for funding for the ACR Imaging Core Laboratory and Dr. Schnall has applied as a co-PI for funding in response to RFA-CA-12-010.

Reviewer 3:

**Strengths:** Dr. Rosen, co-investigator of the project, has applied for funding for the ACR Imaging Core Laboratory as part of a larger consortium, the Imaging and Radiation Oncology Consortium (IROC), which has submitted a request for funding in response a National Cancer

Institute funding notice (RFA-CA-12-014). Dr. Schnall, leader of the ACR Imaging Network and PI for the formula grant has applied for funding in response to RFA-CA-12-010 as co-PI with Robert Comis, M.D., to form the ECOG-ACRIN partnership co-operative group for clinical oncology and advanced imaging trials. Funding is pending.

Weaknesses: None noted.

***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:

The final report indicated that no publication resulted from this project.

#### Reviewer 2:

The grantee presented their results from their prior version of the tool, iPad, at RSNA Annual Meeting 2012, Chicago, Illinois (Rubin D, et al., “ Tools for Quantitative Imaging Assessment of Treatment Response in the American College of Radiology Imaging Network (ACRIN)). They are continuing their analysis of the results of the current tool (ePAD) and comparing them to the earlier tool. The overall outcome is acceptable.

#### Reviewer 3:

Strengths: The grantees are continuing data analysis from the reader study.

Weaknesses: No publication or patent from a rather large research effort.

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

### **COMMENTS ON STRENGTHS AND WEAKNESSES**

#### Reviewer 1:

One master's student participated in this project.

#### Reviewer 2:

The funds from this project were used to pay technologist, imaging analyst, project managers and staff scientists. A graduate student was also trained in this project. It enhanced the quality and capacity for research at the grantee's institution.

#### Reviewer 3:

Strengths: The grantees acquired the EMC Celerra NS-G2 platform which extended the value of their existing EMC CX700 storage array. The grantees trained one new investigator (master student, no salary support from this grant).

Weaknesses: None noted.

***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 PI collaborated with a research team at Stanford University who was responsible for the programming effort.

Reviewer 2:

The grantee established close collaboration with Dr. Daniel Rubin's team at Stanford. The study also involved the participation of radiologists and programmers at both Stanford and University of Pennsylvania.

Reviewer 3:

Strengths: There is a collaboration with Daniel Rubin, M.D., of Stanford University, who led the research team and oversaw the programming efforts of the ACRIN and Stanford programmers. The radiologists who served as readers for the study were from Stanford University and University of Pennsylvania.

Weaknesses: None noted.

### ***Section C. Recommendations***

#### **SPECIFIC WEAKNESSES AND RECOMMENDATIONS**

Reviewer 1:

There is quality and reliability improvement due to the streamlining and integration of the different functions and processes and the generation of a report that can be viewed and exported to clinicians. It would be beneficial to the project if this impact is somehow quantified.

Reviewer 2:

1. Testing the software and technique development in this project for other imaging modalities (PET/CT, MRI) is desirable.
2. More readers and image cases should be included in future studies.
3. Quantitative analysis of image before and after treatment should be thoroughly studied.

Reviewer 3:

1. Aim 3 needs additional data and more compelling data to support the efficiency of the approach. This concern is somewhat alleviated by the fact that the team is strong and the study analysis is ongoing.

2. There are no publications yet from this large effort. The analysis of the reader study needs to be completed and reported in a peer-reviewed journal.