# American College of Radiology

# Annual Progress Report: 2008 Formula Grant

**Reporting Period**

July 1, 2009 – June 30, 2010

**Formula Grant Overview**

The American College of Radiology received $2,144,345 in formula funds for the grant award period January 1, 2009 through December 31, 2012. Accomplishments for the reporting period are described below.

**Research Project 1: Project Title and Purpose**

*Methods and Strategies to Incorporate Radiotherapy Delivery Uncertainties in Clinical Trials Outcome Analysis* - Randomized clinical trials provide evidence-based medicine that has become the foundation of radiation oncology. Numerous technologies are being used to deliver targeted radiotherapy. These technologies all have their own operational characteristics and uncertainties. Significant variations also exist in individual implementation of these technologies. These uncertainties may influence, to a critical extent, the outcome of clinical trials. However, they have not been addressed so far in a systematic manner in the outcome analysis. This study aims at bridging this gap with theoretical methodologies for critical assessment and propagation of uncertainties of radiation deliveries as a complement to current clinical trial analysis. Our hypothesis is that by properly accounting for the delivery uncertainties, we will allow better prediction of outcome.

**Anticipated Duration of Project**

1/1/2009 - 12/31/2012

**Project Overview**

The objective of this study is to bridge a gap between present radiotherapy related clinical trials, where essential delivery uncertainties are not included in the outcome analysis, and computational implementation that has the ability to propagate these uncertainties through the analysis process.

These methodologies will have the ability to propagate the uncertainties that arise from the treatment unit calibration, throughout the treatment process to the outcome. The quantitative analysis model will employ algorithms that enable self-adaptation, definability, and extendibility. The analysis process can also be reversed to create quality assurance guidance for limiting these uncertainties of radiotherapy delivery. Specifically, the tasks include the following:

A. To quantify the uncertainties associated with radiation therapy delivery process with accumulated data, which include identification of key components of the process, such as radiation calibration,

patient setup, etc., where potential variation can occur, uncertainties associated with each component and the accumulative effect from all.

B. To investigate the optimal statistical methods for propagating these uncertainties in outcome analysis modeling. Extensive research has been carried out in the mathematical methods in the uncertainty modeling and the propagation methods. We intend to evaluate the various strategies and algorithms and select the optimum ones that best suit our process.

C. To implement these mathematical methods into established biological modeling open source software system available for radiotherapy researchers. Ample considerations will be given for further extension and adaptation of the open software.

D. To develop a reverse process that can start from the endpoint of the outcome and predict the limit for uncertainties, thereby offering outcome based quality assurance guidelines for the delivery technologies, benefiting future design of clinical trials.

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**Expected Research Outcomes and Benefits**

Randomized clinical trials have been the foundation of modern medicine. They are the cornerstone of radiation therapy development. A large portion of recent development of radiotherapy treatment strategies and techniques is the direct or indirect result from these randomized clinical trials. Collection of appropriate data associated with these clinical trials and the analysis of the data with the most accurate and suitable tools are essential elements to the success of these trials.

There are uncertainties associated with all the processes of the radiotherapy treatments and data collection. The outcome analysis should consider these uncertainties. Many of these uncertainties are addressed in various ways. Among these, the heterogeneity of reporting has been addressed in guidelines and standards for reporting the results from clinical trials. The uncertainty of radiotherapy delivery, with a disconcerting amount of discrepancies reported from institutions (around 30% failure rate from a radiological physics center head and neck phantom test), is however generally not considered in the outcome analysis. These discrepancies and deviation could reach such an extent that they steer the clinical trial outcome, namely, the difference in outcome is found not due to the

medical technique difference for which the clinical trial is designed, but due to the deviation from the trial protocol. There were reports that deviation from radiotherapy protocol had a major negative impact on outcome.

It is therefore essential to access and quantify the uncertainties associated with the individual process of the execution of the clinical trials and evaluate the impact of these uncertainties on outcomes. This is the main focus of this study.

**Summary of Research Completed**

During the last year, we have concentrated our effort in the following main aspects of our project:

A. To quantify the uncertainties associated with radiation therapy delivery process with accumulated data, which include identification of key components of the process, such as radiation calibration, patient setup, etc., where potential variation can occur, uncertainties associated with each component and the accumulative effect from all.

B. To investigate the optimal statistical methods for propagating these uncertainties in outcome analysis modeling. Extensive research has been carried out in the mathematical methods in the uncertainty modeling and the propagation methods. We intend to evaluate the various strategies and algorithms and select the optimum ones that best suit our process.

*The following publications resulted from the studies of "A. To quantify the uncertainties associated with radiation therapy delivery process"*

Data were accumulated from the process of radiation therapy deliveries and the outcomes of some individual steps in that process were analyzed. Quantitative analysis on the uncertainties was sought based on the variations of outcomes with certain amount of accumulated data.

<u>1. Difference between planned dose and delivered dose shown from deformable dose accumulation</u>
The dose delivered to the patient could be different from the dose distribution in planning system because of patient setup variations and organ motions in each treatment fraction. The fraction dose actually delivered to the patient can be estimated using deformable registration between daily setup image and planning image. The estimated fraction doses are accumulated to form the final dose that is delivered to patient throughout radiotherapy treatment. This study aims at a method that employs deformable dose accumulation for the evaluation of the results of intensity-modulated radiation therapy (IMRT) in pelvic cases. Two pelvic IMRT cases were studied where the treatment target were prostate fossa and bladder respectively. The anatomy changes of the critical structures such as rectum, bladder, or small bowel and the planning target volume (PTV) were considered in these cases. Daily cone-beam CT (CBCT) images were used to deform the daily fraction dose to reference geometry, which in our study was the first fraction geometry. A commercial software system, MIMvista (Version 4.2.2; MIMvista Corp., Cleveland, OH), was used to perform deformable image registration and dose accumulation. The dose distributions from deformable accumulation and treatment plan were compared in terms of isodose lines and dose-volume histogram (DVH). Figure 1 shows the DVH for PTV and Organs at Risk (OAR) of the prostate fossa case. Histograms calculated from treatment plan (solid lines) and deformable dose accumulation (dotted lines) are plotted together for

comparison. We can see that there is almost no difference in DVH curves for left and right hips where the motion is almost rigid. In contrast, the DVH in soft tissues was different when the deformable dose accumulation was used. This work was presented at the ICCR 2010 annual meeting.

2. Variation of images registrations from multiple software systems in IGRT

Image-guided radiotherapy (IGRT) is used to minimize the patient setup uncertainty through on-line evaluation. At this point in time, computer-assisted rigid-body registration is commonly used for IGRT. One of the main uncertainties of IGRT procedure is the accuracy of image registration. Quantitative information on the differences of image registration results from multiple systems is needed to provide an estimate of image registration uncertainties since there is no ground truth. The purpose of this study is to re-register IGRT images across different hardware and software platforms and compare results when the IGRT process is repeated. Images and IGRT shift results from three different treatment systems (Tomotherapy, Elekta, Varian) have been sent from various institutions to the Radiation Therapy Oncology Group (RTOG) for evaluation. Three head&neck and three prostate patients' data from the treatment systems were used, and for each patient 2-4 daily image datasets were included. Cases from Tomotherapy were uploaded through Image Guided Therapy QA center (ITC) for de-identification and integrity verification. In all cases, daily shifts were re-calculated from registration of the planning CT with the daily IGRT data using three independent software systems (MIMvista, CMS Focal, VelocityAI). Similar volumes of interest (VOIs) and the same initial positions were used in registrations. Not all systems were able to perform successful registration for all the cases. Only successful registrations were included in comparison. For the head&neck cases, the absolute values of differences of the registration results from different systems were 2.9±2.4mm (mean±SD; range 0.5-8.6mm, left-right (LR)), 2.5±1.3mm (0.5-4.9mm, superior-inferior (SI)), and 2.3±0.9mm (0.3-3.6mm, anterior-posterior (AP)). Out of 21 comparisons in head&neck cases, four (19%) had differences larger than 5mm in any of three dimensions, and ten (48%) had differences larger than 3mm but less than 5mm. For the prostate cases, the differences were 2.4±2.0mm (0.2-8.4mm), 2.2±1.5mm (0.0-5.1mm), and 2.0±1.8mm (0.0-6.3mm), in three dimensions respectively. Out of 24 comparisons in prostate cases, one (4%) had differences larger than 7mm, and seven (29%) had differences larger than 4mm but less than 7mm in any of three dimensions. This work was presented at the ASTRO 2009 annual meeting.

3. Motion control consistency with abdominal compression device from daily 4D CBCT

Abdominal compression may reduce the tumor motion caused by breathing effect. However, the degree of motion control may vary day to day which is the potential uncertainty of this process. 4D CBCT reconstruction provides a tool to assess the motion control for each treatment fraction. In this study, we investigated the motion control consistency during radiation treatment course through 4D reconstruction of daily CBCT images. For the lung cancer patients who were treated with abdominal compression, kilovoltage (kV) CBCT image was acquired for each treatment fraction to correct patient setup. The CBCT imaging data were then reconstructed using a respiratory-correlated technique to derive 4D CBCT images with 10 different phases of a breathing cycle. Daily tumor motion with abdominal compression was evaluated from the 4D CBCT by recording the tumor center position relative to the treatment isocenter in each phase. Data from three patients (1 upper lobe tumor and 2 middle lobe tumors) were included in this study and 4 consecutive treatment fractions for each patient were studied. The extent of tumor motion was compared between different treatment fractions to assess the daily variation of motion control with abdominal compression. Figure 2 shows an example of tumor motion in each of three directions during 4 consecutive treatment fractions.

Mean value and standard deviation of tumor motions from all patients and treatment fractions studied were 3.1mm±0.9mm (mean±SD), 6.8mm±1.7mm, and 5.3mm±1.8mm in LR, SI, and AP directions respectively. The variation of tumor motion extent of the same patient between different fractions was 1.1mm±0.7mm, 2.0mm±1.9mm, and 2.3mm±2.0mm, in LR, SI, and AP directions respectively. This work will be presented at the AAPM 2010 annual meeting.

4. Uncertainty and margin study for IMRT, Volumetric Modulated Arc Therapy (VMAT), and proton beam therapy for treatment after radical prostatectomy

Uncertainties in organ position causes the uncertainties in dose delivered to the organs. In this study, we compared the uncertainties of 3D dose distributions, caused by the geometrical uncertainty of patient setup, in IMRT, VMAT, and proton plans for post-prostatectomy treatment. Four prostate fossa patient datasets were included. For each case three different plans were carried out: an IMRT plan of nine fields (XiO, Elekta), a VMAT plan (Oncentra, Nucletron), and a proton plan with two lateral active scanning beams (Oncentra, Nucletron). The plan robustness analysis function in CERR (Washington University, St. Louis, MO) software was used to simulate the DVH uncertainty with given systematic ($\Sigma$) and random ($\sigma$) shifts in three dimensions. Five different combinations of $\Sigma$ (2-4mm) and $\sigma$ (2-4mm) representing clinical situations were used for all plans. The DVH uncertainty range (upper and lower bounds) was generated by CERR for each setting of $\Sigma$ and $\sigma$ with a certain confidence level (95% was used in this study). More than 98% of PTV was covered by 95% of prescription dose in all plans. The upper bound of PTV V95% was close to 100% in all plans for all $\Sigma$ and $\sigma$ settings. The mean values of lower bound of PTV V95% were 85.4%, 85.0%, and 87.5% for IMRT, VMAT, and proton plans, respectively ($p=0.03$ for IMRT vs. proton, paired samples t-test; $p=0.01$ for VMAT vs. proton; $p=0.36$ for IMRT vs. VMAT). The mean values of ranges (upper minus lower bound) for rectum V45Gy were 7.5% (IMRT), 7.5% (VMAT), 15.6% (proton), and the mean values of ranges for bladder V40Gy were 6.2% (IMRT), 9.2% (VMAT), 12.7% (proton). The proton plans exhibited significantly wider range of rectum and bladder DVHs than those from the other two treatment techniques ($p<0.05$ for both). Even though the proton plans had lower rectum and bladder doses as compared with IMRT and VMAT, with the uncertainty, the upper bounds were approaching similar doses from IMRT and VMAT. Analysis of PTV V100%, rectum V56Gy, bladder V56Gy showed similar comparison results. This study will be presented at the ASTRO 2010 annual meeting.

*The following publications resulted from "B. To investigate the optimal statistical methods"*

A method of combining the uncertainties from multiple sources was studied. Evidence theory was applied to this process to combine the evidences from different sources.

5. Application of evidence theory in radiation oncology outcome analysis

Evidence-based medicine has become the foundation of radiation oncology development. There are different levels of evidence upon which radiation therapy practice is based and those levels of evidence introduce various uncertainties, for instance, epistemic uncertainty and aleatory uncertainty. Among several different mathematical theories that describe uncertainty and provide its measures, the evidence theory is the well-established theory that can handle different types of uncertainty. In this study we applied evidence theory to outcome analysis in radiation oncology and evidence from different sources was combined by Dempster's rule to aid the clinical decision making process. A case study of the "degree of belief" and "plausibility" in regard to the occurrence of pneumonitis in radiation therapy is implemented as an example to demonstrate our application and better statistical

results were obtained. For example, the probabilities of complication from independent random institutions range from 12% to 30%. However, by applying evidence theory the probabilities were better described by belief and plausibility functions which gave a range from 10.6% to 12.3%. This study will be presented at BMEI 2010 conference.

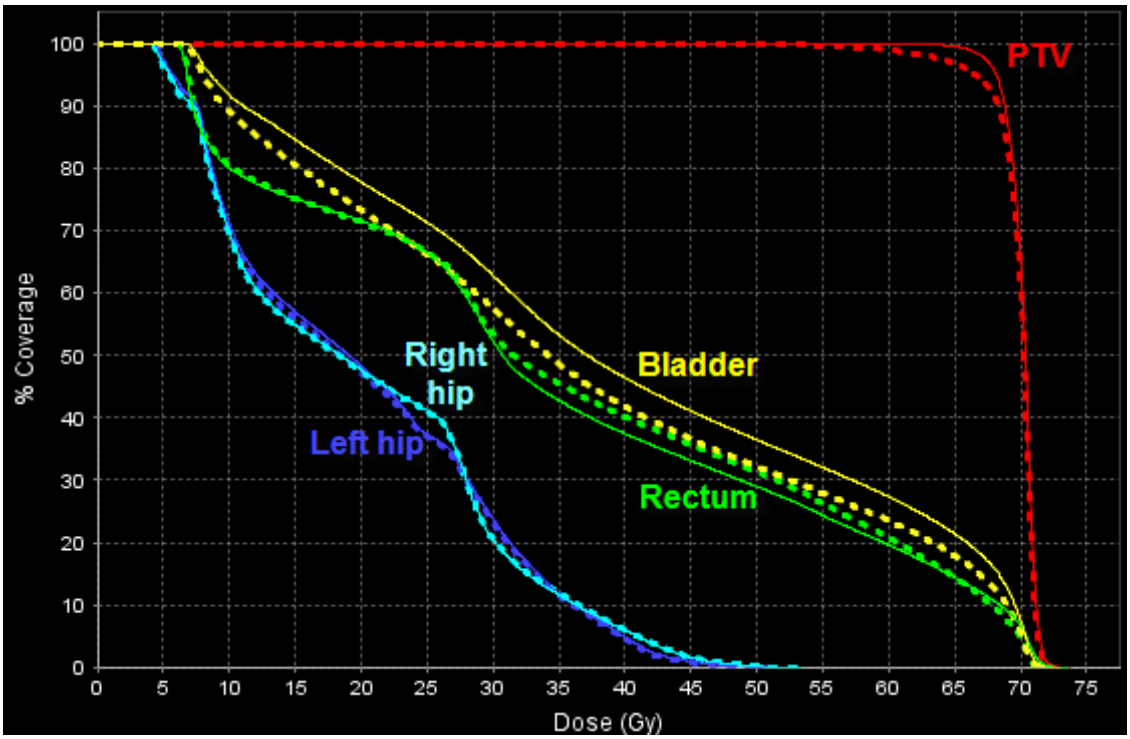


**Figure 1.** DVH for PTV and OARs derived from treatment plan (solid lines) and deformable dose accumulation (dotted lines) in the prostate fossa case.

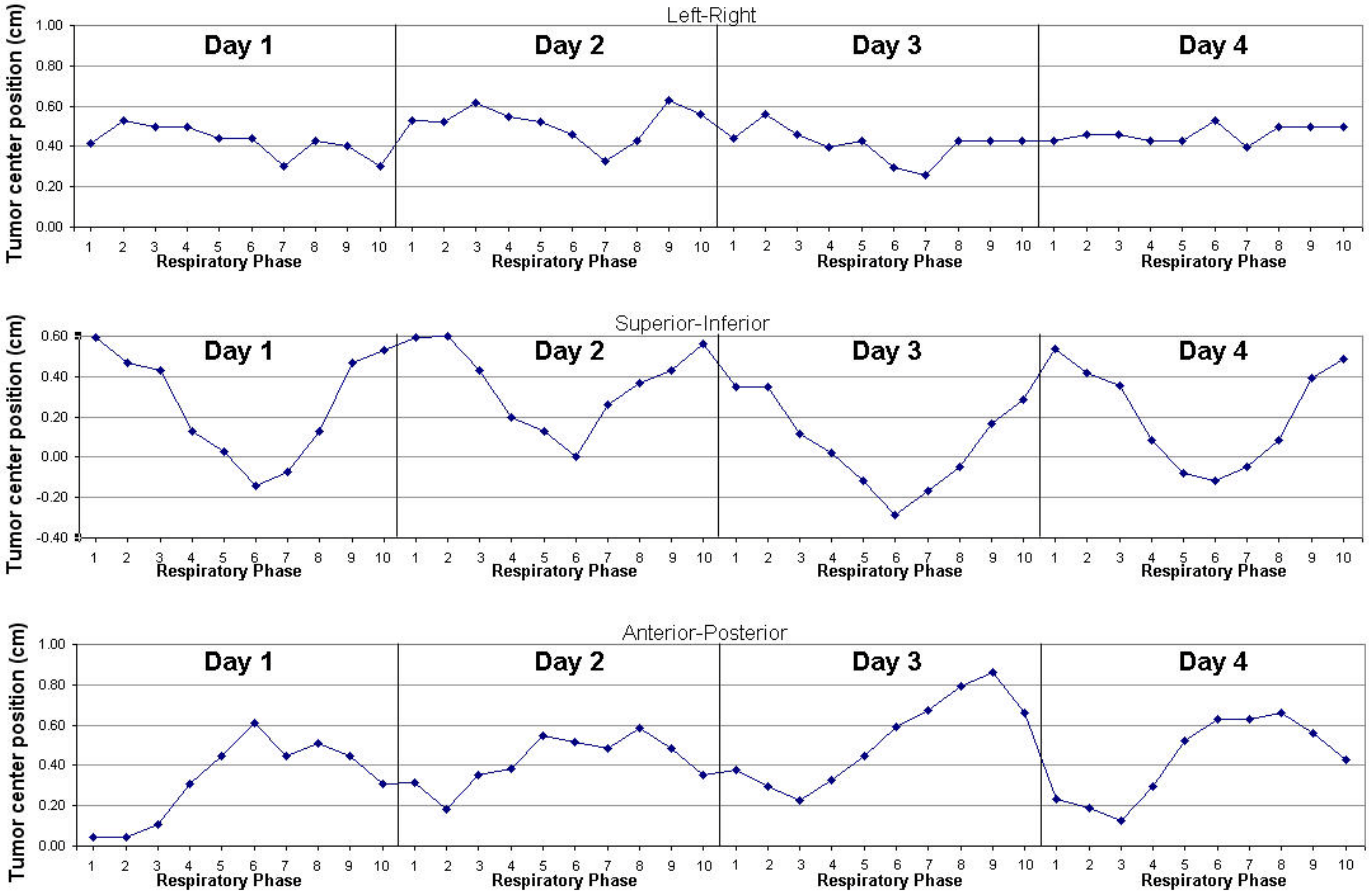


**Figure 2.** An example of tumor motion in three directions during 4 consecutive treatment days. Tumor center position is the offset of tumor center from the treatment isocenter.

## Publications

Y. Cui, J. Piper, J. Galvin, Y. Xiao, "Application of Deformable Dose Accumulation in Pelvic IMRT Cases with Daily CBCT", Proceedings of XVIth International Conference on the Use of Computers in Radiation Therapy (ICCR) 2010, in press

Y. Cui, J. M. Galvin, W. L. Straube, W. R. Bosch, J. A. Purdy, A. Li, Y. Xiao, "Multi-system Verification of Registrations Utilized in IGRT Processes", International Journal of Radiation Oncology * Biology * Physics, 2009; 75(3): S99-S100

Y. Cui, A. Harrison, Y. Xiao, "SU- GG- J- 92: Motion Control Consistency with Abdominal Compression Device from Daily 4D CBCT", Med. Phys., 2010; 37(6): 3166

Y. Cui, A. Harrison, M. Studenski, T. Showalter, J. Deasy, Y. Yu, J. Galvin, Y. Xiao, "Uncertainty and Margin Study for IMRT, VMAT, and Proton Beam Therapy for Treatment after Radical Prostatectomy", Proceedings of the American Society for Radiation Oncology (ASTRO) 52nd Annual Meeting 2010, in press

Y. Xiao, Y. Cui, W. Chen, Y. Hussaini, Y. Yu, J. Galvin, "Application of Evidence Theory in Radiation Oncology Outcome Analysis", Proceedings of 3rd International Conference on BioMedical Engineering and Informatics (BMEI) 2010, in press

**Research Project 2: Project Title and Purpose**

*Development and Analysis of an Infrastructure for Review of Modern Clinical Trials that Include Radiotherapy* - Cooperative group protocols have greatly increased in complexity over the past 15 years. At least for the radiotherapy component of these protocols, this dramatic change has created considerable difficulty when reviewing dose distributions to determine whether protocol requirements have been met. Much of the difficulty is due to the time it takes to review advanced technology protocols. This research study is designed to demonstrate that analysis tools are now available that can shorten the time for case review to the extent that accuracy is not lost in a tradeoff with efficiency. This study will also provide information for designing the review tools needed for future cooperative group protocols that might include one or more advanced technologies such as IMRT, IGRT, SBRT, 4D respiratory control, or deformable image registration using PET and/or MRI.

**Anticipated Duration of Project**

1/1/2009 - 12/31/2012

**Project Overview**

The Radiation Therapy Oncology Group (RTOG) has, over the past two years, gathered state-of-the-art equipment that allows detailed review of radiotherapy dose distributions. However, during a similar time period, there has been a tremendous increase in both the complexity of dose distributions and the overall amount of data that must be analyzed to determine if protocol requirements have been met. These changes place considerable stress on the protocol Principle Investigators (PIs) to review submissions in a timely manner. This research project will compare 2D review techniques (i.e., sequential 2D cross-sectional review to accomplish 3D analysis) used for older 3D-CRT protocols with newer methodologies that allow multi-planar (e.g., coronal, sagittal, and cross-sectional) review of advanced technology protocols. Advanced technology protocols are studies that include Stereotactic Body Radiation Therapy (SBRT) treatments that use a large number of beam directions to achieve highly conformal dose distributions, dose-painting methodologies that include Intensity Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), 4D Respiration Controlled treatment, and the use of deformable fusion. The comparison will be accomplished by simply comparing the average review time for protocols that use the Advanced Technology Consortium (ATC) remote review tool (called QuASA$^2$R for Quality Assurance Submission, Archive, Analysis, and Review System) to the average review time for protocols that use more versatile tools that potentially shorten the review time. Another possible limitation in the ability of PIs to rapidly review large numbers of submitted cases is the firewalls that are established by most institutions to protect information. This is the case for both the American College of Radiology (ACR) and the Image-Guided Therapy QA Center (ITC), the institutions holding the data for the RTOG. Such firewalls hamper the ability of a PI to review cases at will, and it is common practice to instead place

data in a secure area for a limited amount of time at the request of the PI. Improvements in the area of data dissemination for review purposes will be investigated as part of this research.

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**Expected Research Outcomes and Benefits**

Many recent advanced technology treatment modalities have matured to the point where they are being used as part of large Phase III studies that are aimed at accruing in excess of 1,000 patients. Additionally, some studies use more than one advanced technology. For example, there is currently at least one Phase III trial that allows both IMRT and IGRT. The incorporation of these and other advanced technologies in large Phase III studies makes the research described here extremely important. As the number of cases requiring review increases dramatically, there is the possibility that the quality of review could be compromised. In order to avoid a decrease in the level of review for a particular study, it is necessary to improve the efficiency of the review process while maintaining quality. This is the aim of the research plan described here. One way of accomplishing this goal is to identify and implement more efficient case review tools. Another way is to create a case review environment that optimizes the use of existing equipment. In addition, remote review capabilities can be improved to allow for situations where it is not possible for one or more individuals to be involved in a central review process. Thus, this research will study the case review process with the goal of implementing and testing the improvements needed to meet the demands of the cooperative group protocols that utilize advanced technologies.

**Summary of Research Completed**

During this reporting period we have created documents for internal and external work processes for the Reviewers to utilize the software's that are available to them. This has been through feedback from the Reviewers that we are improving the review processes for advanced technology protocols.

Aim: Investigate methods to improve information management capabilities, data analysis tools, and educational facilities for personnel involved in clinical trials so that the overall quality and efficiency of trial execution and outcome analysis is improved.

During this past year, we've concentrated our efforts with this research project in reviewing Stereotactic Body Radiation Therapy (SBRT) treatments that use a large number of beam directions to achieve highly conformal dose distributions, dose-painting methodologies that include Intensity

Modulated Radiation Therapy (IMRT), Image Guided Radiation Therapy (IGRT), 4D Respiration Controlled treatment, and the use of deformable fusion. We are comparing the average review time for protocols that use the Advanced Technology Consortium (ATC) remote review tool (called QuASA$^2$R for Quality Assurance Submission, Archive, Analysis, and Review System) to the average review time for protocols that use more versatile tools that potentially shorten the review time.

We have acquired more review systems that are needed for the clinical trial cases that utilize the latest technologies. The deployment of these systems is also part of the infrastructure design process which is described below.

We are evaluating BrainLab software for neurosurgical planning, as well as systems with Monte Carlo capabilities. For development of needed tools that are unavailable from the commercial systems, we plan to build upon CERR (Computational Environment for Radiotherapy Research).

We've acquired Matlab licenses for numerical computations with matrices and vectors. Mathwork's MATLAB is a high-level language and interactive environment that enables users to perform computationally intensive tasks faster than with traditional programming languages such as C, C++, and Fortran.

Over this past reporting period, we have acquired Elekta Monaco Workstation with IMRT and Volumetric Modulated Arc Therapy (VMAT) Software which is a stand-alone radiation therapy & medical image viewing and treatment planning platform with Monte Carlo and Pencil Beam dose algorithms. This system has biologically-based optimization, smart sequencing, Voxel Definition Controls, Multi-Plan Viewing where we can compare Dose distributions and Dose-volume Histograms (DVH) for up to three alternative plans simultaneously. The Dose Cursor Tool, Summation and subtraction of dose plans, Contouring Tools including Auto-Segmentation, 3D Variable, Margin and Unique Drawing assistant allows the Reviewers to review images more efficiently since some of the Reviewers find this software user friendly. The Real-Time Imaging for final beam arrangement with dose approval, Function, Imaging Tools including Window and Level controls, Synchronized Zoom and Pan with independent Transverse, Sagittal and Coronal viewing has allowed the Reviewers to view the images in multiple views in real time. Since the Reviewers need to evaluate the DVH's, Ports Real-time, and high resolution Digitally Reconstructed Radiographs including Maximum Intensity Projection (Virtual fluoroscopy), this software displays these images in an environment that the Reviewers can evaluate all of this information simultaneously

We've also acquired Nucletron Oncentra for use in evaluating Proton plans which include CT images, structures, and dose constraints.

In addition to the treatment planning systems, we're evaluating Anatom-e XRT Information Systems that provides focused contour maps for every part of the body. This will allow us to go through comprehensive contour guides covering every slice in detail. This aids in standardized, reproducible guide to disease sites in our analyses.

For deployment of these review applications we are exploring TRIAD (Transfer of Images and Data) with CITRIX virtualization application environment, linking to the central Clinical Trials

Management System (CTMS). We have been successful in utilizing CITRIX for our reviewers this past year which has streamlined the review process times.

With our Image Guided Radiation Therapy (IGRT) Reviews we have created IGRT instructional documents for each process to streamline the processes.

We continue to gather data for this project through the input from the Reviewers of the advanced technology data used in clinical trials of the various software's that are made available to them. **We** intend to evaluate the various review processes of the software's that are required to evaluate the advanced technologies of the radiotherapy component of the protocols. The tools now available can shorten the time each Reviewer requires to complete a case review with the highest quality of accuracy and improve overall efficiency. Some of the difficulty is due to the time it takes to review advanced technology protocols. The documents that we've created for the Reviewers have been based on the feedback from Reviewers and we continue to evaluate and improve on the case reviews for advanced technologies. Attachments include the documents that we've created for Reviewers that are utilizing the MiMvista software for IGRT reviews which is advanced technology and the worksheet that the Reviewers complete for the IGRT evaluation. This information from the Reviewers allows us to evaluate the use of the review tools available for advanced technologies used in clinical trials.

## Research Project 3: Project Title and Purpose

*Screening For Depression and Referral for Treatment of Cancer Patients* - The first purpose of this project is to determine the usefulness of screening for depression among cancer patients receiving radiation therapy, in terms of the proportion of patients who are identified as depressed and who are not currently receiving mental health treatment. Patients who are found to be depressed will be offered a referral to a mental health professional or primary care physician, depending on their preference. Three months later, they will receive a follow up telephone interview. The goal is to evaluate the efficiency of screening and to identify and find ways of overcoming the significant barriers to cancer patients receiving care for depression.

### Anticipated Duration of Project

1/1/2009 - 12/31/2012

### Project Overview

*Objective* – Depression is common among cancer patients, but often goes unrecognized and untreated, unnecessarily compounding patients' suffering and further compromising their quality of life. Screening with brief depression questionnaires is widely seen as providing a means of improving detection of depression among cancer patients and facilitating their referral to treatment in either mental health or primary care settings. Yet, questions remain as to whether screening is efficient: most patients who screen positive will not be found to be depressed upon interviewing, and an unknown proportion who are depressed will already be receiving treatment. Evidence is limited, but there is also a concern that many patients who are provided with referrals either do not complete them or encounter significant barriers that prevent them from receiving acceptable, effective care.

*Specific Aims* – To understand the rates of patients who screen positive on a questionnaire are actually found to be depressed in a psychiatric interview and secondly, the proportion who are not already receiving treatment. Third, to provide referrals for treatment to those depressed persons not already and treatment and follow up with them three months later to determine whether they have completed the referral and experienced an improvement.

*Design, Methods* –Four hundred patients who score positive on a measure of depression while they are receiving radiation treatment for cancer will receive telephone interviews to ascertain whether they are depressed, whether they have sought treatment, and, if they are not currently receiving treatment, their treatment preferences, i.e., antidepressants or psychotherapy. They will be provided with an appropriate referral. Three months later, a follow up telephone interview will ascertain if they have completed the referral and whether they have experienced an improvement in their level of depression. If they have not completed the referral or not received effective treatment, the nature of the barriers they encountered and how these could have been overcome will be assessed.

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**Expected Research Outcomes and Benefits**

A full range of effective treatments for depression are available, but the challenges lie in detecting depression in medical patients in a timely fashion and ensuring that they access these effective treatments. Depression is too often missed or not given the priority it deserves. Problems in detecting and treating depression are compounded for cancer patients who are contending with often debilitating treatment for their life-threatening condition. The American health care system is fragmented and the pathways to care for depression are not well mapped, but it is generally understood there are significant barriers to patients accessing care, particularly when they are uninsured or underinsured. Screening with brief questionnaires is seen as one way of identifying depression that would otherwise be missed, but screening does not alleviate depression if it does not lead to completed referrals to effective care. The first outcome of the proposed research will be scientific papers documenting the efficiency of screening for depression in terms of the rates of the disorder that are uncovered. The second outcome will be papers documenting the rate of referrals for treatment, what makes for effective referrals, and what can be done to improve the process, particularly for uninsured, underinsured, and members of minorities. The most important outcome of

the project is that its results will serve as pilot work for an application for a 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.

**Summary of Research Completed**

The study was activated May 28, 2009. One patient was consented but not screened as the study closed July 14, 2009 due to IRB concerns regarding plans for handling patients with suicidal ideation and because the study chair stepped down. A new study chair, Dr. Lynne Wagner, was appointed by the Radiation Therapy Oncology Group (RTOG) and she made substantial revisions as described below. The amendment was reviewed and approved by the NCI. An experienced Structured Clinical Interviews for DSMDisorders (SCID) interviewer was hired and SCID practice interviews have been conducted with the interviewer and Dr. Wagner to ensure protocol adherence and quality of the interviews. The study re-opened July 1, 2010. The RTOG has had exceptional interest from the RTOG sites. Due to the limited funding that supports only a part time SCID interviewer we have determined to open this trial to the Community Clinical Oncology Program (CCOP) sites (since the CCOP grant funds case accrual for this project) in order to manage accrual. The target accrual of 18 per month (~4 per week) would be manageable and we will monitor accrual weekly to ensure an acceptable accrual rate.

Rationale for Study Changes

*Introduction and Rationale*
While the primary objective for the proposed study has not changed, we have revised secondary objectives at the direction of the study team. We have revised the introduction to cite relevant research to support modifications to our secondary objectives. We have revised the Rationale and Justification to reflect our revised secondary study objectives.

*Potential Risks*
Our study team has worked closely with RTOG to establish procedures for the assessment and management of psychosocial distress and suicidal ideation. This was done in response to concerns reported by multiple institutions which came up during IRB review. Multiple institutions reported IRB disapproval due to the lack of a plan for managing suicidal risk and acute distress. We have developed procedures.

*Objectives*
We have revised some of the secondary study objectives. We have expanded the goal of establishing the rate of mood disorders to include dysthymic disorder, adjustment disorder and bipolar disorder, in addition to depression. We have placed increased emphasis on the objective to evaluate screening measures to detect clinically significant distress and accordingly, we have added the National Comprehensive Cancer Network (NCCN) Distress Thermometer as an additional screening measure. Few studies have evaluated the NCCN Distress Thermometer using the SCID for validation and we believe that in doing so, we will contribute to our evidence base in distress screening. In revising the design of this trial, we added a brief questionnaire for sites to complete to summarize the availability of psychosocial services at their institution as the availability of on-site services may affect study endpoints.

Because we are collecting this data, we have added an additional objective to describe psychosocial services at participating RTOG institutions. This will represent one of the largest studies to date that will provide data on the availability of psychosocial services in community settings. Last, we have revised our objective to add our goal of assessing the acceptability and patient interest in receiving psychosocial interventions using novel modalities (e.g., telephone, internet).

*Registration*
We have revised registration procedures to clearly articulate responsibilities of participating institutions. The purpose of doing so was to develop procedures for the management of psychosocial distress and suicidal ideation. This was particularly important as this trial will assess level of distress and thoughts of suicide. Because many participating institutions will not have on-site mental health staff and also because many study assessments will be conducted via telephone, we developed procedures for the management of distress and for the assessment and management of suicide risk.

*Patient Assessment and Outcome Measures*
As stated above, we have added the NCCN Distress Thermometer as an additional screening measure. Many institutions utilize the NCCN Distress Thermometer for clinical service delivery. However, few studies have evaluated the NCCN Distress Thermometer using the SCID for validation. Including this measure in RTOG 0841 will contribute to our evidence base in distress screening.

We have removed the Assessment of Barriers to patient care. We have replaced the previous semi-structured interview with a published, validated 20-item instrument, entitled, The Perceived Barriers to Psychological Treatment (Mohr, Ho, Duffey et al. 2010). In addition, we have added interview questions to assess patients' interest in receiving psychosocial modalities using novel modalities for administration. The rationale for doing so is to obtain data to direct future interventions for psychosocial distress. An increasing number of studies have been published to evaluate telephone-based counseling for distress in cancer and a few studies have examined internet-based support groups. However, we are unaware of any studies to date that have assessed cancer patients' attitudes about receiving psychosocial interventions for distress. As we transition to the utilization of non-traditional clinical service delivery models, data from patients can assist with intervention design.

## Research Project 4: Project Title and Purpose

*Assessment of Methods to Increase Latino Enrollment into Cancer Clinical Trials* - Despite national initiatives to increase the enrollment of racial and ethnic minorities into cancer clinical trials, participation by Latinos remains low. The Radiation Therapy Oncology Group (RTOG), which conducts cancer clinical trials involving radiotherapy, will develop and evaluate evidence-based, cuturally and linguistically appropriate patient education materials and investigator training programs to increase the enrollment of Latinos into cancer clinical trials in Pennsylvania and nationally. We will also use cartographic modeling techniques to do a gap analysis through identification of current RTOG sites and their Latino population density compared to high density areas of Pennsylvania and the United States where we do not have RTOG sites. This will help us strategically identify sites to recruit into the RTOG that will facilitate Latino access to state-of-the-art cancer clinical trials.

**Anticipated Duration of Project**

1/1/2009 - 12/31/2012

**Project Overview**

*Research Objectives:* 1) The RTOG will develop and evaluate evidence-based, cuturally and linguistically appropriate education and awarness programs and recruitment materials to increase the enrollment of Latinos into cancer clinical trials in Pennsylvania and nationally. We will identify 4 RTOG clinical trials to target and evaluate. 2) We will develop and assess cultural competency training for RTOG investigators and research staff. 3) We will conduct a gap analysis of current RTOG sites with high density Latino populations and areas of the Commonwealth of Pennsylvania and the country with high density populations where we do not have RTOG sites. This will help us strategically identify sites to recruit into the RTOG that will facilitate Latino access to state-of-the-art cancer clinical trials.

*Methods:* 1) In consultation with our RTOG investigators and patient advocates, we will identify four protocols and use certified Spanish translators who will do back-forth translations of the informed consents and the study specific and general clinical trials and radiation therapy patient materials. Materials will be developed by our investigators and our in house marketing staff with input from patient advocates. 2) RTOG will develop a Latino Cultural Competency and Recruitment Training Program for physicians and clinical research associates (CRAs) who have primary contact with cancer patients and are located at facilities in geographic regions with Latino populations. The training program will instruct the caregivers in the barriers, myths, beliefs, and norms within the Latino culture that may impede clinical trial enrollment and provide strategies for overcoming these barriers. Video recordings of the training sessions will be made available for subsequent reinforcement of course material and for physicians and CRAs unable to attend in person. An interactive program with role playing will be used in the training sessions. Culturally appropriate Spanish language patient information brochures, posters, and Spanish translations of patient consent forms for RTOG's larger randomized trials will be developed and provided to enrolling facilities. Pre and post knowledge tests will assess effectiveness of the training in enhancing cultural competence. 3) We will use cartographic modeling techniques to do a gap analysis to assist with the identification of current RTOG sites with high density Latino populations and areas of Pennsylvania and the country with high density populations where we do not have RTOG sites.

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**Expected Research Outcomes and Benefits**

This research is designed to address the underrepresentation of Latinos in cancer clinical trials. The primary outcome will be a 10% increase in Latino recruitment by year 3 but we will continue to evaluate recruitment annually past the end of this study. We need to recognize the multifactorial nature of barriers to minority recruitment and that this study is only the beginning of testing evidence-based methods to begin to improve recruitment. Improvements are expected to be incremental with identification of evidence-based methods that show increased awareness, informed consent and accrual to research. RTOG will leverage this funding to continue to support the methods that show efficacy in increasing Latino recruitment. Increased minority recruitment to clinical trials provides the ability to generalize results to the Latino population which is the fastest growing minority in Pennsylvania and the United States. These strategies also enhance social justice by facilitating Latino access to state-of-the-art cancer clinical trials.

**Summary of Research Completed**

Aim #1: Develop and evaluate evidence-based, cuturally and linguistically appropriate education and awarness programs and recruitement materials to increase the enrollment of Latinos into cancer clinical trials in Pennsylvania and nationally.

Aim #2: Develop and assess cultural competency training for RTOG investigators and research staff.

Progress for Aims 1 & 2:
A Latino patient advocate for RTOG has been appointed to the RTOG Patient Advocacy Committee and he attended the RTOG semiannual group meeting in June 2010. We have identified four RTOG protocols to target and are partnering with a Pennsylvania-based firm to develop a training session and recruitment materials to be deployed in spring 2011.

Aim #3: Conduct a gap analysis of current RTOG sites with high density Latino populations and areas of the Commonwealth of Pennsylvania and the country with high density populations where we do not have RTOG sites.

Progress for Aim 3:
As noted in the last report the initial focus has been on the gap analysis. Our research found that, according to the U. S. Census Bureau, Latinos account for approximately 15% of the population. From 2000 to 2006 the Latino growth rate was 24.3%, more than 3 times the growth rate of the U.S. population (of 6.1%). Cancer ranks as the second leading cause of death among Latinos in the U.S. (24%), second only to heart disease. Although the percentage of Latinos in the U.S. has increased dramatically, Latino enrollment in cancer clinical trials does not mirror their representation in the general population. The Radiation Therapy Oncology Group (RTOG), a national clinical trials cooperative group, has a Latino recruitment of 3.3% over the last 5-years.

Employing cartographic modeling techniques a gap analysis was conducted, through identification of current RTOG sites and their Latino population density compared to high density areas in the U.S. where we do not have RTOG sites. We also assessed Latino recruitment to clinical trials by geographic and RTOG affiliate location.

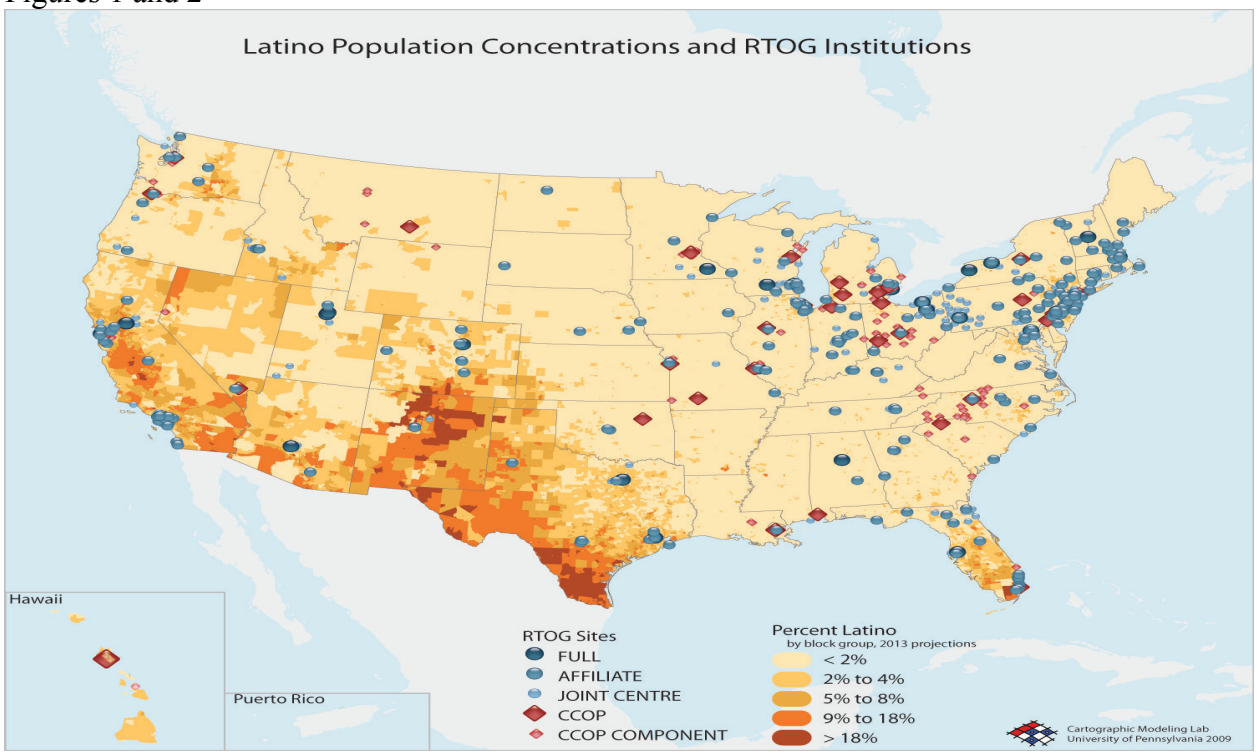
Geographic Information System (GIS), technology was used to spatially analyze data relevant to clinical studies. The maps were made in ArcMap GIS 9.3 software using shapefiles of the United States with county divisions taken from the Economic and Social Research Institute (ESRI) database. The maps were color-coded for Latino population density by county and the members were designated with color-coding by quartile of overall Latino accrual to RTOG trials over the past 5 years. The 717 RTOG participating member sites were designated on the map with different symbols representing full or affiliate status. See Figures 1 and 2.

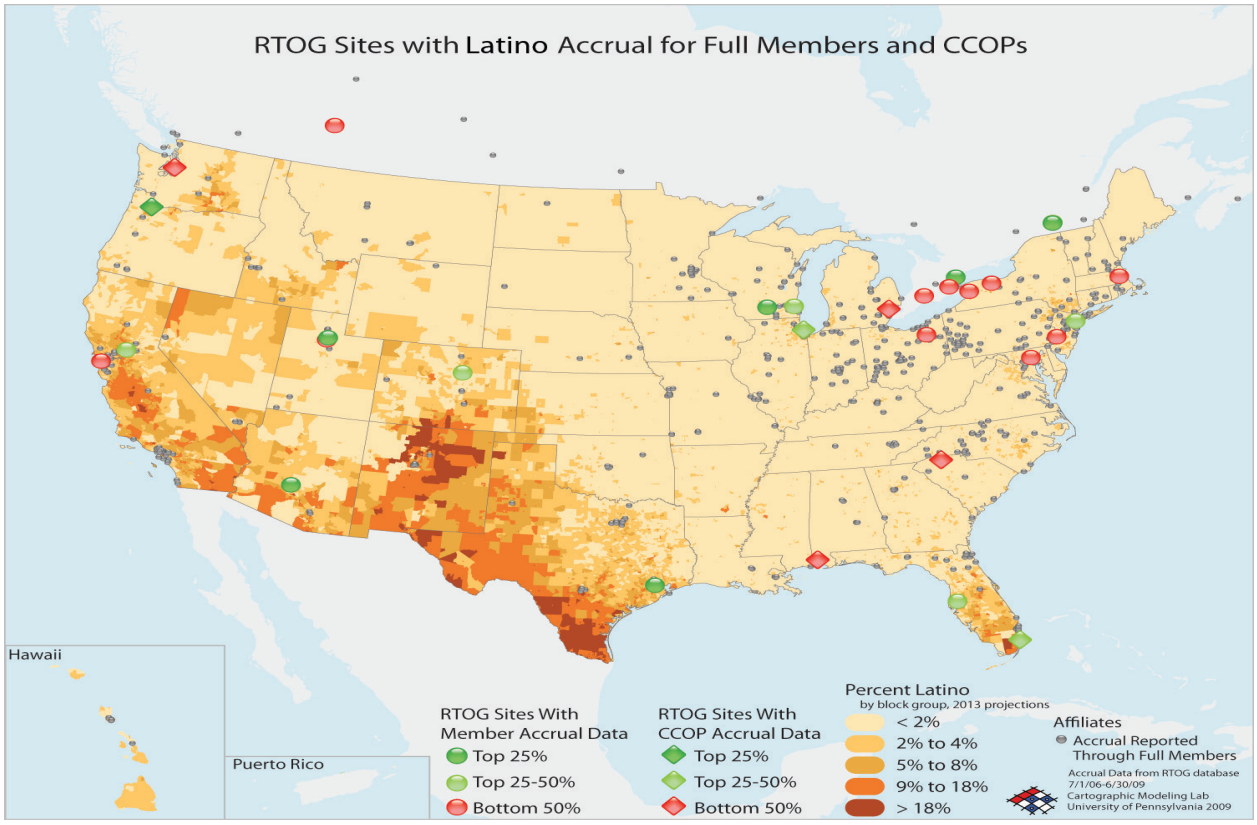
Results: RTOG site locations are most heavily concentrated in the northeast and along the eastern and western seaboards. There are fewer RTOG sites in higher density Latino regions. Of the RTOG sites reporting Latino accrual, mapping indicates that the highest Latino accruing sites to RTOG trials are predominantly not in high density geographic Latino population areas. GIS mapping therefore, clearly depicts a disconnect between Latino population density and RTOG member locations. However, a limitation to the study is that affiliate accrual is reported through the full member or CCOP (Community Clinical Oncology Program) member and their affiliates may be in a somewhat different location.

Conclusion: "A picture is worth a thousand words." GIS mapping has helped identify geographic barriers to Latino accrual including high density Latino population areas without RTOG members. This will help us strategically identify radiotherapy sites to reach out to as new partners in Latino dense locations to facilitate Latino access to state-of-the-art cancer clinical trials. Mapping also identified high Latino RTOG clinical trial accrual in low Latino dense sites which would not have been easily identified without mapping. We plan to contact these sites to determine best practices for Latino recruitment.

This work was recently presented as a poster abstract and the manuscript is in development. Citation: Bruner, J., Stine, S.H., James' J., Heron, D., Curran, W., Bruner, D.W. Using Cartographic Mapping to Assess and Develop Strategies to Improve Latino Recruitment to Radiation Therapy Oncology Group Clinical Trials. Poster Abstract Presentation at NCI-ASCO Cancer Trial Accrual Symposium, Bethesda, MD., April 29-30, 2010.

Figures 1 and 2



## Research Project 5: Project Title and Purpose

*Emerging Imaging Technology Clinical Trials in PA: Reproducibility and Responsiveness of MRI Measures of Body Composition and Lipid Metabolism in Women with Gestational Diabetes* The purpose of the multi-site Pennsylvania study is to evaluate the reproducibility and responsiveness of MRI measures of maternal body composition and lipid metabolism in the assessment of gestational diabetes. The MRI measures to be evaluated are associated with problems and diseases related to processing of blood sugar and obesity.

### Anticipated Duration of Project

1/1/2009 - 12/31/2012

### Project Overview

Previous C.U.R.E. funding established a network of academic medical centers in Pennsylvania (ACRIN PA) with the broad goal of advancing the role of imaging in the detection and/or treatment of disease by conducting early stage imaging clinical trials. This project seeks to continue the work of that network. A multi-institutional clinical trial is proposed to determine the reproducibility and responsiveness of MRI measures of maternal body composition (visceral adiposity, intermuscular adiposity), hepatic steatosis, and intramyocellular lipid concentration. These MRI measures have been shown to be sensitive to insulin resistance and lipid metabolism in a variety of conditions ranging from cardiovascular disease, aging, diabetes, and obesity.

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### Expected Research Outcomes and Benefits

Although the study will focus on gestational diabetes, the proposed MRI techniques are widely applicable to a variety of clinical studies on disorders of obesity and insulin resistance in both children and adults. A major outcome of this study is the creation of a multi-center Pennsylvania based network that can provide advanced MRI techniques for the study of adiposity and disorders of lipid metabolism. Availability of these techniques will facilitate clinical and translational research.

**Summary of Research Completed**

After considerable evaluation of the feasibility of this proposed trial and current conventions for the clinical care of these patients, the scientific review team determined that this project would not be successful given concerns raised by the prospective sites about MRI research scanning of pregnant subjects. This assessment was made during an initial exploration of regulatory approval at participating sites. No funds have been expended on this project to date. An alternative project, which has been under development, has been identified by the scientific leadership and will be submitted to the Department of Health for review and approval.

**Research Project 6: Project Title and Purpose**

*Remote Review of Quality of Radiation Treatment for Lung Cancer: A Pilot Project* - Definitive radiotherapy is the standard therapeutic approach for inoperable lung cancer. However, this treatment can potentially result in fatal treatment complications. The purpose of this pilot project is to develop methods of collecting clinical data directly from distinct electronic medical record systems at a variety of radiotherapy facilities to assess quality of treatment delivery in lung cancer. The clinical data will be standardized and aggregated in a central database from which queries will be performed to retrieve critical data. The methods developed will assure secure transfer, review, and analysis in compliance with regulatory requirements. The overall goal will be to scale this approach for automated collection of quality of care data across multiple institutions to analyze and improve radiation treatment delivery for lung cancer patients.

**Anticipated Duration of Project**

1/1/2009 – 12/31/2012

**Project Overview**

The hypothesis: Despite significant barriers to full interoperability, it will be possible to demonstrate remote secure access to Radiation Oncology Electronic Medical Records, to remotely retrieve clinically significant quality of care data on lung cancer patients, to remotely aggregate these at a central secure super server, and conduct initial analyses of these quality data to evaluate quality of Radiation Oncology delivered.

Specific Aims include demonstrating the feasibility of collecting and aggregating in a central database established quality parameters for workup and radiation treatment of lung cancer from multiple institutions with different Electronic Medical Records (EMR) systems, validating the de-identification engine and confirming secure HIPAA compliant internet-based data transfer and software interoperability, performing data extractions on the aggregated data and analyzing quality parameters, and demonstrating compliance with the larger connectivity goals of the NCI Ca-BIG in clinical Radiation Oncology.

The investigators will develop a core data set description to implement parallel processes and systems for radiation oncology facilities using the two different EMR systems. To facilitate the study and re-use of these data, the repository will follow and model the principles of the cancer Biomedical

Informatics Grid (caBIG) and its related technologies, including the consistent definition and translation of data elements to NCI-defined ontologies and taxonomies. Where ontologies and taxonomies are undefined by caBIG (e.g., for radiotherapy delivery data), the researchers will cooperate with the vendors and standards bodies to define structure and vocabulary that will facilitate research against the unified database.

In the current project, another process will be required wherein a data upload from each vendor system to a super-server will result in an aggregate of combined datasets. A requirement of this process will be that data from each vendor's dataset will be mapped and/or converted to standard caBIG-compliant data elements. In addition, software tools will be required to assure data quality and integrity, to provide data quality reports back to each of the vendors, and to provide outcome and analysis reports to Quality Research in Radiation Oncology (QRRO).

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**Expected Research Outcomes and Benefits**

At the present time, only 3% of all patients with a diagnosis of malignancy are enrolled into clinical trials. The therapeutic outcome data for the remaining 97% of patients is usually not collected and is rarely put to rigorous data analysis to identify predictors of outcome. One approach to overcome this obstacle is to aggregate and query data from multiple treatment sites so a more robust analysis on the larger patient population can be performed. We propose in this project to develop an approach to standardize and aggregate data at a remote site on lung cancer patients at multiple institutions receiving radiation treatment. The radiotherapeutic management of lung cancer is a rapidly evolving field with newly validated quality measures that correlate with likelihood of cure as well as toxicity. This approach could then be used to identify new measures of treatment outcome and quality of radiation treatment delivery. The ability to analyze larger, aggregated data on lung cancer patients would allow for identification of critical treatment parameters that would not be apparent on analysis of smaller subsets of patients. This will allow comprehensive assessment of quality of care during treatment and for recent time periods. Patients will benefit from a more timely quality of care assessment system. The long-term goal of this project would be to improve the baseline standard of radiotherapeutic treatment of lung cancer patients.

**Summary of Research Completed**

As stated in the Strategic Research Plan the Specific Aims were:

Specific Aim #1: To demonstrate the feasibility of collecting and aggregating in a central database established quality parameters for workup and radiation treatment of lung cancer from multiple institutions (approximately 20) with two different widely used Radiation Treatment Electronic Medical Records (EMR) systems.

Specific Aim #2: To validate the de-identification engine and confirm secure HIPAA compliant internet-based data transfer and software interoperability.

Specific Aim #3: To perform data extractions on the aggregated data set interrogating patient demographic, tumor specific, and radiotherapeutic treatment parameters from any lung cancer patient receiving or having received radiation treatment at a participating institution and to analyze the data to establish baselines for quality parameters.

Specific Aim #4: To demonstrate that this method of remote access and aggregation will be compliant with (and the first example of) the larger connectivity goals of the NCI Ca-BIG in clinical Radiation Oncology.

The investigators have worked towards achieving Specific Aim 1, 2, and 4. Several aspects of the planning process were more complex than originally anticipated. The quality parameters that can show meaningful indicators for individual patients were found to require a set of data elements to measure them that is more extended than the original proposal assumed. The database to support these measures requires data elements beyond those already included in the existing individual databases of each of the electronic medical record (EMR) systems. Information from the images and dose distributions in the patients may need to be characterized even though the images and radiation therapy objects will not themselves be extracted from the separate electronic systems Treatment Planning Systems. The Quality Research in Radiation Oncology (QRRO®) was conducting studies during this time period that provide useful information on quality measures for this project and the investigators sought to benefit from those findings. The initial planning stage for this project required additional steps and more time than the original plan anticipated before the data gathering and collation could proceed and achieve the specific aims.

The milestones from the Strategic Research Plan are shown below:

1/1/2009-6/30/2009: Identify established quality parameters for workup and treatment of lung cancer and define measurement of these parameters based on data fields in two Electronic Medical Records (EMR) systems. Assure that data fields needed for quality of care measurement comply with requirements for de-identification of data according to the Health Insurance Portability and Accountability Act (HIPAA). Establish central QRRO database on a server in ACR Philadelphia and identify collaborating institutions for study. Identify potential legal and regulatory issues from vendors and collaborating institutions. Collaborate with centers for approvals and IT

interactions/permissions. Establish contractual agreements with vendors with regard to confidentiality and other issues.

Investigators have made progress by defining quality parameters for workup and treatment of lung cancer and defining the specific data fields needed to measure those quality parameters. They have assured that the data fields would comply with requirements for compliance with HIPAA regulations. They have worked to resolve the legal and regulatory issues for vendors and institutions. These tasks and others in this first milestone have required more time to complete than the original schedule anticipated but they can be successfully completed.

7/1/2009-6/30/2010: Conduct data gathering and collation to populate central database with data from approximately 20 practices using two EMR systems. Design and develop secure internet-based interoperable software tools to facilitate remote analysis and review of aggregated data on quality of care. Perform analyses on the aggregated data so as to establish comparability of data across systems and practices and measure baselines for quality of care parameters. Identify remaining barriers to these goals. Perform the first demonstration of proof of principle that this method of remote access and aggregation can be the first example of the larger connectivity goals of the NCI Ca-BIG in clinical Radiation Oncology. Identify potential lack of connectivity to CaBIG root causes, such as adapter compatibility.
Investigators have made progress on developing the data base and software tools but these tasks are not completed. The new timeline for this project aims to complete these tasks by 6/30/2011.

Although progress has been made on the planning milestones for the first two time periods, the specified milestones have not been achieved as scheduled for several reasons, including initial delays in notification of funding approval, the need for more complex planning with additional steps, and the desire to use information derived from the ongoing QRRO project. The original schedule was aggressive in planning for the first 18 months of the study with a much more limited set of tasks for the rest of the four year period. The tasks originally scheduled for the first 18 months are now projected to take 30 months. Because the original schedule for the later periods was much less aggressive than for the early period, investigators will still be able to achieve the study aims within the four year time period.

The principal investigator will assure that progress is more rapid in the revised plan for achieving the milestones by adopting more explicit project management tools and providing a regular schedule for all key participants to communicate and update the status and management of tasks, progress, problems, pending items, and results.