

American College of Radiology

Annual Progress Report: 2009 Formula Grant

Reporting Period

January 1, 2010 – June 30, 2010

Formula Grant Overview

The American College of Radiology received \$2,043,960 in formula funds for the grant award period January 1, 2009 through December 31, 2013. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Novel Methods for Cancer Clinical Trial Design and Analysis - Clinical trials provide the critical evidence necessary to advance treatment for cancer. With the ever growing number of promising interventions, there is a need for improvements in trial design in order to a) obtain answers more quickly, b) conserve and optimize resources, and c) make better choices of what treatments to pursue in further evaluation. In addition, as treatment regimens become more complex and multimodal, the ability to accurately characterize whether anticipated benefits with respect to specific disease event reduction have occurred requires extensions of standard analytic methods. To address these needs, we propose a series of methodological projects aimed at addressing current questions in clinical trial design and analysis. These projects encompass a range of needs that apply broadly to cancer clinical trials and research in general.

Anticipated Duration of Project

1/1/2010 - 12/31/2013

Project Overview

Three specific investigations are proposed as follows:

Aim 1: Development and Use of an Efficient Phase II/III Transition Design – The traditional paradigm for therapy development involves a pilot safety and efficacy trial (phase II) followed by a definitive Phase III comparative trial if warranted. This development model is intensive with respect to the time and logistical overhead involved in conducting sequential studies, and too often leads to failure in Phase III despite promising Phase II data on seemingly similar targeted populations. We propose to evaluate and implement a novel Phase II/III transition design that has thus far been little used in the oncology setting.

Aim 2: Alternative Metrics for Time to Event Endpoints in Phase II and III Trials – Phase II trials have traditionally been formulated as one-sample designs where all patients receive the treatment

of interest. While statistical power for comparison to fixed benchmark values can be adequate within a feasible sample size, the design suffers from dependence on historical comparisons that may not prove reliable. An alternative is a randomized Phase II design, where either a) treatment arms are not formally compared, but rather the arm that prevails to any degree is taken as more favorable with respect to further development, or b) adequately powered comparisons for simple endpoints such as fixed-time proportions failure-free are feasible. We propose analytic development of an approach using quantile (median, etc) estimation and comparison in the randomized Phase II setting. The approach is equally applicable to Phase III trials, and may have particular advantages in the presence of non-proportionality.

Aim 3: Estimating Treatment and Covariate Effects Under Competing Risks – Competing risks, whereby patients are subject to multiple potential failure types, with only one of these occurring as the primary first failure, are ubiquitous in cancer. In addition to multiple cancer-specific events (i.e., local, regional, distant recurrence), patients may experience second primary cancers or deaths from other causes that preclude any cancer event. While correct estimation of event-specific probabilities of occurrence for competing risks is straightforward, inference in the presence of competing risks remains more challenging. We propose to investigate and compare different recently developed competing risks modeling methods.

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Expected Research Outcomes and Benefits

Cancer clinical trials are a critical component of cancer care and as all reliable treatment options arise through this process, it is only through systemic and comprehensive evaluation in a trial setting that the risks and benefits of any option can be assessed. However, the process can be slower than desired, is always process intensive, and requires the greatly valued contribution of patient participants, who are seeking the best possible option for their personal situation while at the same time contributing to research. In addition, an increasing array of agents in which to try in some disease settings further strains the development system. A more efficient treatment evaluation strategy could improve both knowledge acquisition and patient care. Previous proposals to accelerate the development process have often been too ambitious, and remain unused. We propose three areas of research that have immediate practical implications for cancer clinical trials. The integrated Phase II/III design fits well into the current framework while at the same time offering the opportunity to improve it, and thus is more likely to become widely used.

More informative and reliable endpoints for Phase II trials are needed, as typical response endpoints often fail to correlate adequately with survival and also do not fully apply to many modern therapeutic agents. Analytic methods that can more directly assess risks, benefits, and effects on intended targets will increase the efficiency of trials and produce more informative reports. This investigation will provide a concrete demonstration of the worth of these innovative concepts, furthering knowledge in cancer research and treatment.

Summary of Research Completed

Aim 1: Development and Use of an Efficient Phase II/III Transition Design

Integrated (also known as seamless) phase II/III trial designs implement the phase II and phase III portions of clinical development into a single trial, using information from the phase II portion in the subsequent phase III trial. Despite a body of literature discussing the merits of integrated phase II/III clinical trial designs within the past two decades, implementation of the designs has been limited in oncology studies. In this reporting period, we first reviewed the differences among proposed integrated phase II/III designs.

We then evaluated the efficiency of the integrated phase II/III design in the setting of a multi-center cooperative group, compared to the traditional approach. The evaluation criteria included the effects on required patients and time-saving, using a RTOG trial under development for illustration. These findings altogether with a discussion on practical issues that should be considered before using integrated phase II/III designs, have been documented in a manuscript, titled as “Integrated phase II/III clinical trials in oncology”. This manuscript was submitted to Cancer Investigation in March 2010. Some revisions are needed based on review feedback from the editor and four reviewers, for resubmission. Currently, we are working on the revision and expect to re-submit in late August.

Research Project 2: Project Title and Purpose

Exploration of the RTOG Clinical Trial Database – Beyond Protocol-Specified Endpoints - For over 40 years, the Radiation Therapy Oncology Group (RTOG) has been funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. Drawing upon this vast resource of demographic, treatment, outcome, and patient-reported data, the researchers will develop hypotheses and explore correlations that were not defined in the treatment protocols for patients with brain, cervix, gastrointestinal, head and neck, lung, and prostate cancer. These analyses may lead to future protocols and/or better ways to identify high-risk subgroups and screen patients for specific treatment regimens.

Anticipated Duration of Project

1/1/2010 - 12/31/2013

Project Overview

RTOG investigators complete analyses and report on the endpoints specified in each NCI-approved protocol. Frequently these analyses raise questions or point to other potential hypotheses that were not included in the original protocol. Likewise, current literature and new research may point to areas of interest or possible correlations that were unknown during the design of the original protocol. The broad objectives of this research proposal are to (i) generate hypotheses and explore correlations that may lead to more efficient clinical trials and more patient-targeted treatments, and (ii) explore novel ways of analyzing the demographic (age, gender, race), treatment (including dose, volume, duration), outcome (survival, disease-free survival, time-to-progression), and quality of life (frequency/severity of adverse events, patient-reported outcomes) data in the RTOG database to potentially develop new tools for determining the best treatment regimen for each patient based upon their personal profile.

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Expected Research Outcomes and Benefits

The identification of pre-treatment patient characteristics and demographics associated with better or worse outcome for cancer patients may allow future researchers to generate new hypotheses to address outcome disparities due to age, race, ethnic origin or gender. Exploring the radiation therapy dose volume histogram data in more detail will help with better definitions of dose constraints in future trials. In addition to aiding in the conduct of clinical trials, this type of research may help to tailor treatments to individual patients based on their demographic and/or treatment characteristics profile.

Summary of Research Completed

Aim #1 Generate hypotheses and explore correlations that may lead to more efficient clinical trials and more patient-targeted treatments

Aim #2 Explore novel ways of analyzing the demographic (age, gender, race), treatment (including dose, volume, duration), outcome (survival, disease-free survival, time-to-progression), and quality of life (frequency/severity of adverse events, patient-reported

outcomes) data in the RTOG database to potentially develop new tools for determining the best treatment regimen for each patient based upon their personal profile.

Two secondary analyses have been started in this progress report period. The first is assessing the impact of per protocol defined PSA complete response (PSA-CR), defined at the end of external beam radiotherapy (EBRT) and short-term hormonal therapy (STHT), on treatment outcomes for patients treated on RTOG 9413 “*A Phase III Trial Comparing Definitive Whole Pelvic Irradiation Followed by a Conedown Boost to Boost Irradiation Only and Comparing Neoadjuvant to Adjuvant Total Androgen Suppression (TAS)*”. The second is evaluating associations between V10 and V20 (volume of bone marrow receiving 10 and 20 Gy) and hematologic toxicities for patients treated on RTOG 0418 “*A Phase II Study of Intensity Modulated Radiation Therapy (IMRT) to the Pelvis +/- Chemotherapy for Post-operative Patients with either Endometrial or Cervical Carcinoma*”. Abstracts of these analyses were submitted to the 2010 American Society of Therapeutic Radiation Oncology (ASTRO) annual meeting and both have been accepted for oral presentation at the ASTRO annual meeting in Nov 2010.

Research Project 3: Project Title and Purpose

Emerging Imaging Technology Clinical Trials in PA: Comparison of Full Field Digital Mammography with Digital Breast Tomosynthesis Imaging: Comparison of Recall Rates - The purpose of this multi-center study, to be conducted as part of the American College of Radiology Imaging Network – Pennsylvania, is to evaluate the digital breast tomosynthesis screening recall rates compared to routine 2D projection digital mammography. The goal is to understand if a hybrid combination of 3D tomosynthesis and low dose 2D digital mammography can significantly reduce the recall rate of women from screening mammography without a concomitant reduction of sensitivity of cancer detection.

Anticipated Duration of Project

1/1/2010 - 12/31/2013

Project Overview

Previous C.U.R.E. funding established a network of 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 evaluate the impact of breast tomosynthesis on the recall rate of screening mammography.

Study Hypothesis: Digital breast tomosynthesis (DBT) will improve the specificity of breast cancer screening as measured by a reduction in the recall rate while maintaining the sensitivity of cancer detection. This improved accuracy will be achieved by the optimization of the imaging sequence and number of views obtained at a capped radiation dose in the combined DBT and 2D screening sequence.

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Expected Research Outcomes and Benefits

Screening mammography has been extensively criticized for the high rate of false positive interpretations, a subgroup of which is the recall of patients for additional diagnostic imaging for “pseudolesions” or superimpositions of normal tissue, perceived on screening mammography to be potentially significant lesions that on additional imaging prove to be normal. With competing parameters of specificity and sensitivity, mammographic screening must both limit missed cancers and reduce false positive call-backs. Tomosynthesis, a new emerging technology that allows the 3D reconstruction of images, has shown early evidence suggesting that it could significantly reduce the rate of false positive recalls from screening without a loss of sensitivity or breast cancer detection.

There are few published trials on breast cancer screening with tomosynthesis partly because the optimal procedural metrics for tomosynthesis have not been fully defined. Manufacturers have different platforms that offer different views, different angles, and different dose and exposure levels. The exact number of tomosynthesis views of the mediolateral-oblique (MLO) view only or both MLO and cranio-caudal (CC) tomosynthesis views varies while the screening imaging sequence with or without 2D digital mammography remains controversial. This disparity in image number and image acquisition parameters may alter the balance between specificity and sensitivity and significantly affect radiation dose. The expected outcome of this research is to show that the incorporation of tomosynthesis in the screening paradigm can reduce the number of false positive interpretations without a loss of cancer detection. This improvement in screening specificity must be gained while limiting both the number of imaging views and the radiation dose to the patient.

Summary of Research Completed

Milestone for 1/1/2010-6/30/2010: Complete study design, draft protocol, and seek sites to participate.

In the six months since receiving the 2009FY funding, an executive (protocol) team has been established to develop the study from initial concept to full trial protocol. It includes representatives of the two sites which will enroll to the study as well as experts from a several disciplines who have been involved with other digital mammography and breast tomosynthesis trials. The team designed the trial to answer questions related to image combinations and quality in pursuit of reduced radiation exposure from tomosynthesis technology. The trial design was also vetted with the members of the ACRIN Breast Committee on the monthly conference call.

The ACRIN PA 4006 protocol, *Comparison of Full-Field Digital Mammography with Digital Breast Tomosynthesis Image Acquisition in Relation to Screening Call-Back Rate*, was submitted to and approved by the American College of Radiology Institutional Review Board. The initial aims included in the grant submission were further refined and include:

Primary Aim

To compare recall rates of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Group A].

Secondary Aims

To compare sensitivity of FFDM to the limited DBT set (digital breast two-view tomosynthesis with low-dose MLO) [Groups A and B].

To assess lesion-type characterization:

1. To compare the sensitivity and specificity by lesion-type characterization (calcification-only lesions versus soft-tissue lesions, as well as lesion subgroups: masses, calcifications, architectural distortions, asymmetries) in FFDM versus DBT (two-view tomosynthesis set with low-dose MLO) [Group A call-back cohort and Group B].
2. To estimate the agreement of FFDM and DBT with the determination of the adjudication committee on lesion-type characterization.
3. To use the sequential interpretation results [Groups A and B] in order to compare the two-view limited tomosynthesis set (with low-dose MLO view alone) with the tomosynthesis plus set (low-dose MLO view plus addition of low-dose CC view) on the basis of:
 - Call-back rate;
 - Identification of new lesion(s);
 - Lesion characterization; and
 - Triangulation.
4. To calculate and compare the radiation dose of the FFDM and the DBT sets.
5. To identify the determinants of participant radiation dose and clinical image quality, including factors such as kVp, mAs, target/filter combination, and breast thickness and composition.

The full protocol is available at: www.acrin.org/4006_protocol.aspx

Two Pennsylvania sites have been selected to participate in the study: Albert Einstein Medical Center and University of Pennsylvania Health System, given their familiarity with breast tomosynthesis and previous research in the area.

As the last site for this study was identified, it was necessary to contract with them through March 2013, in order for them to have adequate time to identify patients and complete the study. Therefore, the Study end date has been changed to December 31, 2013.

Resulting Milestone changes:

Milestone(s) for 7/1/2012-12/31/2012: Continue participant follow-up, data cleaning, Quality Control (QC), and analysis.

Milestone(s) for 1/1/2013-06/30/2013: Complete participant follow-up, data cleaning, QC, and analysis.

Milestone(s) for 7/01/2013-12/31/2013: Final analysis and abstract preparation.

Research Project 4: Project Title and Purpose

Investigation and Analyses of Patient Co-Morbidities in a Survey of Radiation Oncology Facilities in the USA and their Association with Treatment Decisions in Radiation Oncology -

The purpose of this project is to describe the distribution of co-morbidities by socio-demographic characteristics such as age, race, geographic region, insurance status and socio-economic status in patients diagnosed with cancer of the breast, cervix, stomach, lung and prostate, to investigate the association of the prevalence of co-morbidities with treatment decisions and variations in compliance with recommended disease management guidelines for such patients, and to examine the interaction of co-morbidities by site and stage of disease with gender, race, and age.

Anticipated Duration of Project

1/1/2010 - 12/31/2013

Project Overview

Since 1973 the American College of Radiology (ACR) has conducted retrospective surveys of the processes of care in radiation oncology through the Quality Research in Radiation Oncology (QRRO, formerly Patterns of Care Study). Detailed information is collected from chart reviews on patient and tumor characteristics, imaging, treatment planning, surgery, radiation and systemic therapy with the purpose of measuring quality of care and comparing care actually received by patients to well-established clinical guidelines. These guidelines base treatment recommendations on tumor and patient characteristics, but provide little guidance on including patient co-morbidities in the treatment decision.

Although co-morbidities are not part of the scope of the QRRO study, the current data collection has included detailed data on co-morbidities for patients treated for breast, cervix, gastric and prostate cancers and non-small cell and limited stage small cell lung cancers. This project will investigate co-morbidity data in detail including interaction with other patient characteristics and association with treatment decisions.

SPECIFIC AIMS

1. To describe the distribution of co-morbidities by socio-demographic characteristics such as age, race, geographic region, insurance status and socio-economic status in patients diagnosed with cancer of the breast, cervix, stomach, lung and prostate.
2. To investigate the association of the prevalence of co-morbidities with treatment decisions and variations in compliance with recommended disease management guidelines for such patients.
3. To examine the interaction of co-morbidities by site and stage of disease with gender, race, and age.

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Expected Research Outcomes and Benefits

This project will provide new information on the effect of co-morbidities on treatment decisions for cancer patients and the interaction of co-morbidities with other patient and tumor factors. This will help fill a knowledge gap in the application of nationally recognized treatment guidelines that currently allow vague exceptions to the established standard of care for patients who have multiple confounding medical problems. By providing analyses that help increase understanding of the impact of co-morbidities on treatment decisions, this project will help improve the standard of care for these patients.

Summary of Research Completed

In the six month period of this report, January 1- June 30, 2010, key research personnel assessed initial data checks and validations embedded in the web-based data entry software of the original Quality Research in Radiation Oncology (QRRO) data collection, defined more complex data validations, and wrote SAS computer programs to validate data elements collected on co-morbidities and other variables in the study that will be used for this project. They also wrote computer programs to calculate basic descriptive statistics for the raw data. They ran these programs for all cases in each study as of the end of May 2010. For any cases with exceptions to the validation rules, the data elements involved in the validation were checked to ascertain whether the data included an error or whether it was a valid exception to the rule. Corrections were made if justified and were documented by the database audit trail. Approximately 150 additional cases were collected by the QRRO study for the database in June and validations for these cases are pending until final closure of the database which is expected in July. Defining,

programming, and running validations and making corrections as needed are the first steps toward achieving this project's Specific Aims.

The milestone in the Strategic Plan for the project for this time period (1/1/2010-6/30/2010) was: Conduct data validations of co-morbidity data for all cases in each study.

This milestone has been completed except for validation of the last 150 cases.

The number of eligible cases by disease site is shown in Table 1.

Disease Site	# of cases
Breast	442
Cervix	262
Prostate	414
Lung	484
Gastric	250