AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6691

Monitoring and Predicting Breast Cancer Neoadjuvant Chemotherapy Response Using Diffuse Optical Spectroscopic Imaging (DOSI)

A phase I/II novel technology multi-center translational study

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PARTIAL PROTOCOL—CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL

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CONFIDENTIAL

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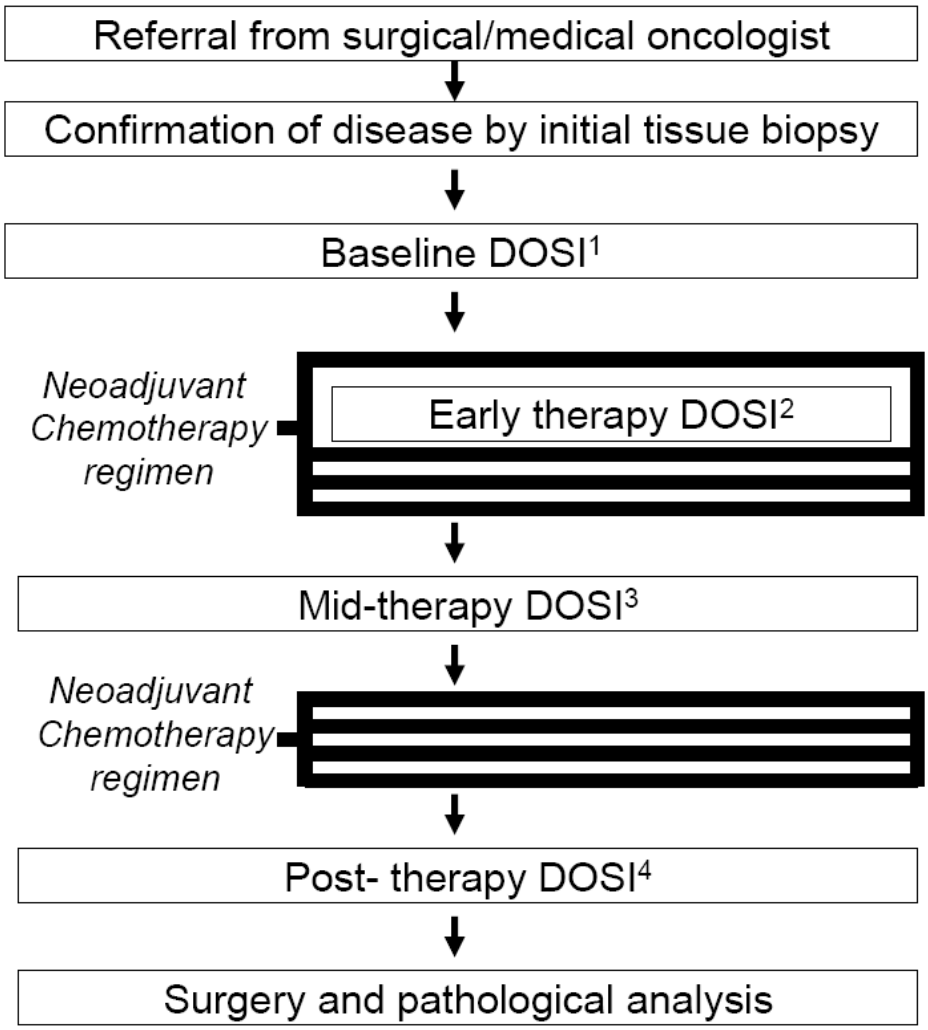
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6691: Monitoring and Predicting Breast Cancer Neoadjuvant Chemotherapy Response Using Diffuse Optical Spectroscopic Imaging (DOSI)

SCHEMA



[1] Baseline DOSI (DOSI-1) must be performed at least two weeks post biopsy and within two (2) weeks prior to initiation of therapy protocol. DOSI and standard of care imaging will be collected.

[2] Early-therapy DOSI (DOSI-2) must be performed 5-10 days after the initiation of the first cycle of the chemotherapy.

[3] Mid-therapy DOSI (DOSI-3) must be performed halfway through the therapy protocol and at least five (5) days after completion of the last chemotherapy prior to the mid-point, and prior to the first chemotherapy cycle after the mid-point or change in chemotherapy regimen.

[4] Post-therapy DOSI (DOSI-4) must be performed after completion of chemotherapy and prior to surgery.

STUDY OBJECTIVES

The primary aim of this clinical trial is to determine whether the baseline to mid-therapy changes in the DOSI measurement of the quantitative tumor tissue optical index (TOI) can predict final

complete pathologic response in breast cancer patients undergoing pre-surgical neoadjuvant chemotherapy. The secondary aims investigate the correlation between additional DOSI quantitative measurements of tumor biochemical composition obtained at other time points, the full range of pathologic response (i.e. complete, partial, and non-response) and any corresponding imaging measurements. DOSI and MR volumetric imaging measurements will be collected.

ELIGIBILITY

Women who have been diagnosed with breast cancer by clinical breast examination, by standard of care diagnostic imaging, or by initial tissue biopsy (confirmed by the local site pathologist); and are scheduled to receive neoadjuvant chemotherapy followed by surgery are eligible for this trial.

SAMPLE SIZE

A total of sixty (60) patients will be enrolled in this imaging study. Five (5) NCI Network for Translational Research in Optical Imaging (NTROI) clinical sites with identical DOSI instruments and procedures will participate in this trial. Additional sites may participate with DOSI units of identical technology and equivalent performance. After six months to set up and open the trial, it is anticipated that accrual will be completed in two years with approximately three (3) patients enrolled per month.

1.0 ABSTRACT

This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

There is considerable interest in developing imaging protocols to monitor and predict breast cancer response to neoadjuvant chemotherapy (NAC), both prior to and as early as possible during the course of treatment. The efficacy and practicality of conventional imaging approaches in the NAC setting varies and identifies the need for alternate functional imaging strategies. Diffuse optical spectroscopic imaging (DOSI) is an experimental imaging method that allows patients to be followed from baseline through treatment and surgery with a cost-effective, bedside, handheld scanning probe. This protocol will evaluate a harmonized DOSI technology platform that has been standardized for NAC monitoring under the NCI Network for Translational Research in Optical Imaging (NTROI) U54 cooperative agreement. DOSI is an academic research platform that has been verified by NTROI investigators and their respective institutional review board (IRB) committees as a "no significant risk" (NSR) device, meeting Food and Drug Administration (FDA) criteria for exempt status. Studies will be performed in specified clinical sites on approximately 60 neoadjuvant chemotherapy (NAC) patients. In preliminary NTROI patient studies conducted over the past 5 years, our investigation team has shown DOSI quantitative functional endpoints to be effective in monitoring and predicting tumor response to neoadjuvant chemotherapy. In the current protocol, we will employ standardized clinical measurement and standardized analysis procedures. As a primary aim, we will evaluate whether a quantitative DOSI tissue optical index (TOI) can predict NAC pathologic complete response (pCR) by the mid-point of the therapy regimen. Our secondary aims are to examine additional quantitative DOSI endpoints at multiple time points during NAC and to correlate DOSI with other standard of care imaging and/or any magnetic resonance imaging (MRI). As non-invasive DOSI endpoints are obtained rapidly with no risk/discomfort, this experimental imaging modality could be used as a surrogate marker of pathologic response which has been an established indicator of long-term survival. Our long-term goal is to provide oncologists with a relatively simple, risk-free bedside tool that can be used to help inform medical decisions on chemotherapy regimen, duration, and timing of surgery, thereby maximizing therapeutic response and minimizing unnecessary toxicity.

2.0 BACKGROUND AND SIGNIFICANCE

Neoadjuvant chemotherapy (NAC) offers unique opportunities for patient care and cancer drug development [Jones,*et al.*, '06; Gralow,*et al.*, '08; Wolff,*et al.*, '08]. Sometimes referred to as "preoperative systemic therapy," NAC often leads to improved breast tissue conservation and avoidance of mastectomy due to the reduction of pre-surgical tumor size [Fisher,*et al.*, '97]. Importantly, pathological complete response (pCR) strongly correlates with patient survival [Fisher,*et al.*, '02; Gajdos,*et al.*, '02]. Consequently, if tumor response to therapy could be reliably assessed *in vivo* on an individual patient basis, oncologists could potentially optimize treatment strategy and improve patient outcome.

NAC clinical response assessment is predominantly determined by serial physical exam, mammography and/or ultrasound. A recent study evaluating palpation, mammography,

ultrasound and magnetic resonance imaging (MRI) showed 19%, 26%, 35%, and 71% agreement, respectively, with final pathological response [Yeh,*et al.*, '05]. Anatomical changes in tumor presentation are not reliable predictors of final pathological state [Feldman,*et al.*, '86; Helvie,*et al.*, '96; Vinnicombe,*et al.*, '96]. Functional measurements of tumors from contrast-enhanced MRI [Warren,*et al.*, '04; Hylton, '06], Magnetic Resonance Spectroscopy (MRS) [Chenevert,*et al.*, '00; Meisamy,*et al.*, '04], and Positron Emission Tomography (PET) [Mankoff,*et al.*, '03; Kim,*et al.*, '04; McDermott,*et al.*, '06] have shown substantial improvement over conventional anatomic imaging. However, these techniques are difficult for advanced stage cancer patients as they involve both lengthy scan times and exogenous contrast agents, and are of particular concern if frequent measurements are desired.

Currently only morphological criteria are clinical care standards for evaluating therapeutic efficacy [Tardivon,*et al.*, '06]. Recent studies report mixed results showing the value of proliferation biomarkers as predictors of therapeutic response [Assersohn,*et al.*, '03; Bozzetti,*et al.*, '06; Burcombe,*et al.*, '06; Dowsett,*et al.*, '07]. However, evidence suggests that early (24 to 72 hours) tumor biochemical changes that precede volumetric changes in response to cancer therapies are important [Symmans,*et al.*, '00; Archer,*et al.*, '03]. These early biochemical changes in apoptosis and proliferation processes may be important for classifying final pathological outcome [Archer,*et al.*, '03]. In addition, some pre-tumor functional states, such as hypoxia, have been clinically associated with resistance to chemotherapy [Greijer,*et al.*, '04].

Scheduling difficulty and cost considerations often exclude frequent and early monitoring by standard imaging. However, the emergence of dose-density strategies, drug cocktails, multi-stage therapies, and targeted therapies imply that it may become critical to monitor each therapy stage such that the treating physician can "tune" treatments towards individual response. Early functional classification of therapeutic effectiveness, preferably a few days post-treatment, could increase patient survival and minimize unnecessary damage to sensitive tissues (e.g. heart, liver, brain) caused by ineffective therapeutic strategies. However, to date, pathological complete response (pCR) remains the best known predictor of improved survival [Kaufmann,*et al.*, '07]. Thus from an imaging standpoint, a critical challenge is to develop accurate imaging predictors of pCR and pathological non response (pNR).

2.1 Diffuse Optical Spectroscopic Imaging (DOSI)

The use of model-based photon migration methods to quantitatively separate light absorption from scattering in multiply-scattering tissues is a type of near-infrared spectroscopy (NIRS) broadly referred to as diffuse optical spectroscopy (DOS) [Bevilacqua,*et al.*, '00; Jakubowski,*et al.*, '09]. The relationship between DOS and diffuse optical imaging (DOI) is comparable to that of magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI), where DOS typically samples a lower number of spatial locations with high spectral bandwidth (~650 to 1000 nm). DOS and DOI methods have been under development in academic and industry laboratories for approximately 20 years. Both methods have been shown to be safe and effective for *in vivo* imaging and several commercial NIRS devices are sold or under development. However, no commercial system has the technically advanced, broadband capabilities of the bedside, handheld DOSI system proposed in this study. Importantly, the Diffuse Optical Spectroscopic Imaging (DOSI) platform technology for the ACRIN 6691 study has been "frozen" and optimized over the past 5 years for NAC monitoring under the NCI Network for Translational Research in Optical Imaging (NTROI) U54 cooperative agreement. Five identical DOSI platforms with identical software and analysis methods have been distributed to each of

the original ACRIN 6691 sites. Additional DOSI units have been manufactured with identical technology and equivalent performance. Previously established standardization and validation methods continue to be performed at sites, therefore limiting variability between platforms.

We recently reviewed features of DOS and DOI, and the formation of spectroscopic image maps using DOSI [Tromberg,et al., '08; Tromberg,et al., '08]. From a practical point of view, DOSI can be used to form quantitative image maps of local tissue concentrations of oxy-hemoglobin (ctO2Hb), deoxy-hemoglobin (ctHHb), water (ctH2O) and bulk lipid. From these parameters, a tissue optical index (TOI) has been derived: TOI = ctHHb x ctH2O/ lipid that provides high contrast and sensitivity to chemotherapy response.

DOSI measurements of hemoglobin reflect the status of tissue microvasculature [Liu,et al., '95] and may be a direct measure of angiogenesis [Tromberg,et al., '00; Pogue,et al., '01; Zhu,et al., '05]. Changes in tumor hemoglobin concentration have been measured for chemotherapy agents known to possess anti-angiogenic capabilities [Cerussi,et al., '07]. Tissue concentrations of water and lipids are substantially different in breast cancer versus normal tissue [Taroni,et al., '04; Cerussi,et al., '06], and we have shown that DOS can reveal unique cancer-specific absorption signatures not found in normal breast [Kukreti,et al., '07]. Changes in breast tissue water and lipids have been associated with long-term alterations during neoadjuvant chemotherapy as seen with both DOS [Jakubowski,et al., '04] and MRI [Jagannathan,et al., '98]. Finally, we have demonstrated that DOS-measured tumor water concentration and water binding state scale with the Nottingham Bloom-Richardson histopathology score and may be proportional to tissue cellularity and extracellular matrix composition [Cerussi,et al., '06; Chung,et al., '07; Chung,et al., '09].

2.2 Potential advantages of Diffuse Optical Spectroscopic Imaging in Therapeutic Monitoring

DOSI provides macroscopically averaged tissue absorption and scattering properties at depths up to several centimeters. Consequently, the resolution of DOI methods is on the order of a few transport scattering lengths (~5mm to 1cm) [Gandjbakhche,et al., '94; Boas,et al., '97; Pogue,et al., '06]. However, the potential limitations of DOI/DOS in localizing small lesions are not important in characterizing NAC response in large, palpable stage II-IV tumors. This is due to the fact that DOSI is inherently a functional imaging technique that is highly sensitive to endogenous biochemical composition and tumor pathological response [Cerussi,et al., '07]. Although DOSI parameters lack the specificity of conventional gene or protein-based biomarkers, DOSI measurements report on tissue vascular and cellular physiology and metabolism. These quantitative functional endpoints are easy to interpret and provide objective measures to predict therapeutic outcome and minimize patient toxicity.

A practical advantage of DOSI is that it can be administered frequently at the bedside in unconventional settings such a doctor's office or infusion center. The current design is a mobile device which offers increased portability and accessibility. With greater access and cost-effectiveness, DOSI has the potential to improve the clinical management of breast cancer. DOSI is relatively simple to perform and interpret compared to technologies such as mammography, MRI, and PET. Because of its size and portability, DOSI is a low barrier-to-access technology, creating new opportunities for patients to receive personalized treatment, and for physicians to gain new insight into response mechanisms.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

3.1 Primary Aim

3.1.1 To determine whether the percentage change in the DOSI measurement of the tumor/normal (T/N) tissue optical index (TOI) from baseline to mid-therapy is predictive of the final pathologic response (i.e. pathological complete response or non-complete response) of the primary tumor in patients with locally advanced breast cancer;

3.2 Secondary Aims:

3.2.1 To investigate whether change of TOI measurements from baseline to post-therapy is predictive of the final pathologic response (i.e. non-, partial, and complete);

3.2.2 To investigate whether baseline TOI measurements associate with final pathologic response (i.e. non-, partial, and complete);

3.2.3 To investigate whether change of TOI measurements from baseline to early-therapy is predictive of the final pathologic response (i.e. non-, partial, and complete);

3.2.4 To investigate whether TOI measurements at baseline, change from baseline to mid-therapy, and change from baseline to post-therapy correlate with available MRI volumetric imaging measurements;

3.2.5 To explore whether additional optical endpoints and indices obtained during DOSI measurements can be used to predict final pathologic response (i.e. non-, partial, and complete).

3.2.6 To determine a cutpoint for the percent change of TOI from baseline to mid-therapy that is predictive of pathological complete response.

4.0 STUDY DEVICE INFORMATION

4.1 Study Device

This protocol will evaluate a harmonized DOSI technology platform that has been standardized for NAC monitoring under the NCI Network for Translational Research in Optical Imaging (NTROI) U54 cooperative agreement. DOSI methods are based on near-infrared spectroscopy (NIRS), a non-ionizing, non-invasive method widely used for several decades. NIRS has been shown to be safe and effective for *in vivo* imaging and several commercial NIRS devices are sold or under development. DOSI is a technologically advanced form of NIRS that has been under development in academic laboratories for approximately 20 years. The current DOSI platform has been "frozen" for ACRIN 6691 trial and the ACRIN 6691 study will be performed in specified clinical sites using identical DOSI instruments and methods. Additional DOSI units have been manufactured with identical technology and equivalent performance. As an academic research platform, DOSI has been verified by NTROI investigators and their respective IRB committees as a "no significant risk" (NSR) device which satisfies FDA criteria for exempt status.

4.2 Study Device Procedures

DOSI measurements are made with a laser breast scanner (LBS). This bedside-capable system combines frequency-domain photon migration with steady-state tissue spectroscopy to measure complete (broadband) NIR absorption and reduced scattering spectra of breast tissue *in vivo*. DOSI measurements are made by placing the hand-held probe on the tissue surface and moving

the probe to discrete locations along a grid pattern at 1.0 cm intervals. The portable high-bandwidth FDPM instrument employs intensity-modulated diode lasers and conventional steady-state lamps as sources and an avalanche photodiode as the detector. The time required to perform an FDPM measurement depends on the desired precision and number of sweeps. At present, approximately 5 seconds are needed to record data from typical tissues at a given wavelength and position. Several locations are probed and total measurement time ranges from approximately 15 to 45 minutes depending on the number of sites mapped. A standardized mapping scheme will be used for all sites.

As the instrument is a portable device, DOSI may be used at different locations in the institution at the request of the study oncologist and/or radiologist. It is anticipated that DOSI scanning will be performed primarily in the Radiology Departments at each participating institution.

DOSI scanning will be performed by a trained DOSI technologist at each site. Training sessions have been provided and a certification of competence will be completed prior to trial activation. Additional resources have been provided and include an imaging manual, online instructions, online support tools, and phone-in support.

Figure 1 –DOSI instrument (left), with a blowup of the handheld probe (middle). The DOSI instrument is a handheld, single spatial point spectroscopic imager that combines discrete frequency-domain and broadband steady-state spectrometers, with a schematic of the device (right).

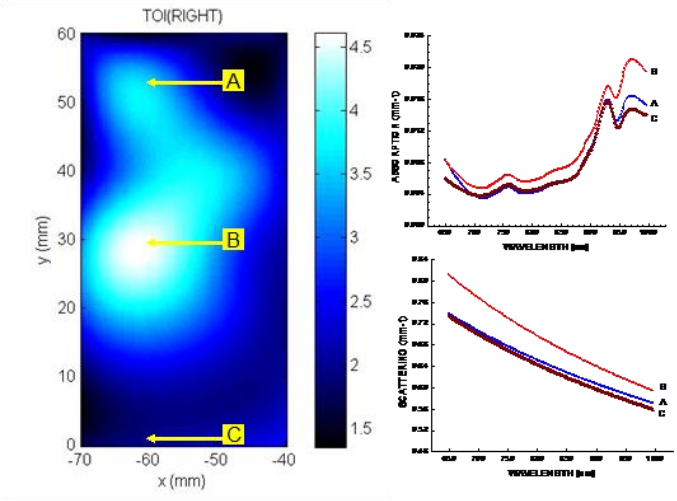


Figure 2 – Diffuse optical imaging may be used to create images from a subset of wavelengths. A 13mm diameter tumor from a pre-menopausal patient is shown on the left panel and is marked with the letter B. The same tumor's NIR absorption and reduced scattering spectra obtained by DOSI non-invasively is shown on the two graphs.

4.3 Current Status of Device and Future Development

Advances in DOSI technology have increased significantly over the past decade and current incarnation of the device has taken advantage of these developments in several smaller trials. Over the past five years, different designs in the technology have been developed and the clear

advantages of each prototype have been incorporated into the current design. The commonality between these designs has allowed the current platform to be the lower barrier of access for a multicenter trial. The current device will include data from all infrared wavelengths, which will allow an easy reference point for other technologies that map functional changes in a neoadjuvant setting. The current design will allow the optimal acquisition of the data set and subsequent analysis will be used to better characterize the pharmacodynamics of neoadjuvant chemotherapy. The laser breast scanner is a bedside-capable system that combines frequency-domain measurements with steady-state broadband tissue spectroscopy to measure complete broadband quantitative near-infrared (NIR) absorption and reduced scattering spectra of breast tissue *in vivo*. Multiple track measurements over the tumor will allow consistent measurements and avoid the confusion associated with interpreting imaging data.

Additionally, the current device has been standardized and a cloned version of the current design has been distributed to the five participating institutions. Additional DOSI units have been manufactured with identical technology and equivalent performance for additional site participation. This standardized DOSI platform will be used in conjunction with other imaging measurements and will be incorporated in the secondary analysis. This multidisciplinary effort is expected to provide new insight regarding the biochemical processes of breast disease and practical approaches for addressing several key challenges in breast cancer.

4.4 Regulatory Status of Current Device

The FDA has characterized the current device as a 'no significant risk' technology (NSR), similar to other near infrared technologies. The study principal investigator (PI) has previously received a specific dispensation clause from each participating institutions' IRBs and each respective IRB has reviewed and approved previous DOSI protocols. Currently, there is no commercial distribution of the component. This study will demonstrate the feasibility of DOSI in a neoadjuvant setting to advance the technology for future wider distribution, with the reproducibility of results showing clinically significant predictive value in a larger multicenter trial.

4.5 Rationale for Device in the Study Population

In the development of imaging technology, the balance between different parameters is dictated largely by the strengths of the application and the needs of the population. The potential population benefiting from this system would be patients diagnosed with locally advanced breast cancer. The necessity to track neoadjuvant chemotherapy response in breast cancer tumors in this population has been identified, as it is estimated that approximately 30% of women with locally advanced breast cancer will not respond well to neoadjuvant therapy [Kuerer, HM et al, 2000, Esserman, L et al, 2004]. As most of the decisions in this treatment scheme are done at the end of chemotherapy, an early functional predictor of response could vastly improve patient outcomes. This concept of monitoring the response of neoadjuvant chemotherapy has been proposed as the optimal way to evaluate which patient will respond to chemotherapy prior to surgery. The optical imaging system being proposed for multicenter studies should provide both molecular absorber information and tissue structural information. Early DOSI pilot studies have indicated that changes in tumor absorption can be observed within the first days after treatment [Cerussi, A. et al, 2007; Tromberg, B. et al, 2005; Shah, N. et al, 2005; Choe et al, 2005; Jakubowski, D.B., et al, 2004]. The surface scanning approach using DOSI is practical application of the technology in this population undergoing neoadjuvant therapy as most tumors are large and sufficiently close to the breast surface to permit optical imaging. The clinical goal in using DOSI would be to

accurately determine response in neo-adjuvantly treated breast patients. The low cost and portability of the optical devices would make them an ideal too for "bedside" response evaluation in this setting.

4.6 Rationale for Imaging Time Points for Device

Early monitoring of response to neoadjuvant therapy is important for the optimal clinical management of the patient. The determination of pathological response by early monitoring will allow clinicians to make go/no-go decisions and explore different treatment options. With discrepancies between clinical response assessments and pathological response, early quantitative measurements of biochemical changes associated with treatment response would provide valuable information. Other functional imaging modalities, such as contrast-enhanced MRI, MRS, and PET have been utilized to show early functional response prior to anatomical changes in both breast cancer and other diseases [Chenevert,et al., '00; Meisamy,et al., '04 ; Mankoff D.,et al., '03; Kim,et al., '04; McDermott,et al., '06]. As these techniques can be difficult to perform in patients with advanced cancers, DOSI provides an opportunity to quantitatively measure the biochemical responses.

The DOSI time points will include a baseline measurement prior to chemotherapy, an early time point within a few days of initiating chemotherapy, and imaging at both mid-therapy and post-therapy. The baseline imaging will be done at least two weeks post biopsy to minimize inflammatory effects from the biopsy. As the rationale for early- and mid-therapy DOSI time points, other functional measurements of tumors from contrast-enhanced MRI [Warren,et al., '04; Hylton, '06], MRS [Chenevert,et al., '00; Meisamy,et al., '04], and PET [Mankoff,et al., '03; Kim,et al., '04; McDermott,et al., '06] have shown substantial improvement over conventional anatomic imaging at similar early time points. In a NIR study, Jakubowski [2004] showed significant changes in optical properties showing rapidly proliferating components of the vasculature and more immature components regress within a few days of initial treatment. Early DOSI pilot studies have indicated that changes in tumor absorption can be observed within the first days after treatment [Cerussi, 2007; Tromberg, 2005; Shah, 2005; Choe, 2005; Jakubowski, DB, 2004] and that the specificity of these changes can be as high as 95%–100%. These studies suggest that noninvasive, quantitative optical methods that characterize tumor physiology may be useful in assessing and optimizing individual response to neoadjuvant chemotherapy.

5.0 STUDY OVERVIEW

This study is a joint effort between ACRIN and the NCI Network for Translational Research of the Interdisciplinary Research Consortium. All sites will use NTROI standardized DOSI specifications and procedures and will collect SOC and/or other MRI imaging, and standard-of-care histopathology to assess pathological response. Five NTROI clinical sites with identical DOSI instruments and procedures will participate: University of California, Irvine, University of California, San Francisco, University of Pennsylvania, Dartmouth, and Harvard/MGH. Additional sites will be provided DOSI devices with identical technology and equivalent performance to meet accrual.

Patients will be recruited by referring surgical oncologist and/or medical oncologist at each participating institution. All participants who consent to participate in the study will receive neoadjuvant chemotherapy, as prescribed by the local site oncologist. Participants who meet eligibility criteria will be able to join the study, regardless of chemotherapy regimen and may be prescribed targeted therapy regimens and immunotherapy during the study.

Breast cancer disease will be diagnosed by clinical breast examination, by standard of care imaging, or by initial tissue biopsy (confirmed by the local site pathologist). Additional dimensionality in the data may be provided by integrating the functional information of DOSI with MRI, which may provide some structural information and functional vascular flow information.

DOSI measurement will be obtained at four scheduled time points through the study:

- DOSI-1 (baseline): At least two weeks post biopsy and two weeks prior to the start of neoadjuvant chemotherapy. The baseline DOSI scan may be performed even on the same day as the first chemotherapy cycle.
- DOSI-2 (early-therapy): Within five (5) to ten (10) days after the first chemotherapy regimen.
- DOSI-3 (mid-therapy): Mid-therapy DOSI (DOSI-3) must be performed halfway through the therapy protocol and at least 5 days after completion of the last chemotherapy prior to the mid-point, and prior to the first chemotherapy cycle after the mid-point or change in chemotherapy regimen.
- DOSI-4 (post-therapy): After the completion of last cycle of chemotherapy and prior to surgery
- Optional DOSI time points: Additional optional DOSI measurements may be obtained through out the chemotherapy treatment regimens.

If available, MRI volumetric imaging will be obtained at participating institutions and these data will be collected for secondary analysis. Additional standard of care imaging will be collected. Clinical endpoint of tumor response will be determined by pathology obtained from surgery in order to classify individuals as complete, partial or non-responders.

As DOSI remains experimental, these early imaging results are not yet fully understood. The experimental imaging results should not and will not change the participant's treatment course and will not be part of the medical record.

5.1 Clinical Response

Clinical response will be determined at the completion of therapy in the ACRIN 6691 study. This standard practice for patients receiving neoadjuvant chemotherapy in breast cancer allows pathologic analysis of surgical specimens collected after the completion of chemotherapy. ACRIN 6691 will use pathologic response for clinical response e.g., the presence or absence of tumor cells in the surgical specimen post chemotherapy. As per accepted criteria (Wolmark, 2001), a pathologic complete response (pCR) is defined as the absence of viable invasive tumor or lymph node involvement of the post-therapy surgical specimen during histopathologic review. This histopathologic analysis will be performed at the treating site and will be reviewed at the ACRIN 6691 Pathology Core Lab at UCI. The presence of residual non-invasive cancer (DCIS) in the absence of viable invasive cancer is still considered a pCR. A dichotomous variable of pCR or non-pCR will be used for primary aim analysis.

5.2 Data Acquisition and Analysis

Optical: DOSI methods for tumor analysis have been standardized and are based on quantitative tissue spectroscopy. Briefly, the DOSI handpiece is scanned in specified grid pattern on patient in reclining position with no compression. DOSI measurements include tissue concentrations of oxygenated hemoglobin (ctO_2Hb), reduced hemoglobin (ctHHb), water (ctH_2O), and lipid. Indices of tissue oxygen saturation (ctO_2Hb/ ctO_2Hb + ctHHb), total hemoglobin (ctO_2Hb +

ctHHb), and the tissue optical index (TOI= (ctHHb x ctH_2O)/lipid) will also be calculated. The wavelength-dependent tissue scattering parameters, A and B, i.e. the "pre-factor" and "scatter power" are calculated. DOSI methods for data acquisition, optical property calculation using model-function fits, and phantom calibration are standardized by the NTR. Each site has identical standardized instruments and software. Raw DOSI patient and phantom data are automatically transmitted to and stored on a central NTR data server. Data are analyzed by software that performs model-based calculations by team members from each NTR site. Calculated DOSI data will be stored on NTR and ACRIN servers.

Clinical: Clinical progression/regression will also be monitored after each round of therapy by physical exam, e.g. palpation of clinical response to therapy. Standard of care imaging will be used prior to therapy and post-therapy as prescribed. Clinical endpoints are "complete, partial or non-responders" determined by pathology following surgery.

5.3 Data Management

All imaging data including DOSI measurements, standard of care imaging, MRI scans, and clinical evaluations will be transferred from the participating institutions to both the NTROI at UC Irvine and to ACRIN. DOSI data will be processed by NTROI using standardized methods and the processed data will be sent to the ACRIN Biostatistics and Data Management Center. Processed DOSI data will be made available to participating institutions via NTROI/ACRIN. Additionally, MRI data will be sent to the NTROI server and the ACRIN Image Management Center for standardized data analysis. Processed MRI data will be made available to participating institutions via the NTROI. Clinical data will be archived by the NTROI and made available to the ACRIN Biostatistics and Data Management Center.

6.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

- **6.1.1** Female;
- **6.1.2** Diagnosis of invasive breast cancer by clinical breast examination, by standard of care diagnostic imaging, or by initial tissue biopsy (confirmed by the local site pathologist);
- **6.1.3** Planned primary systemic (neoadjuvant) chemotherapy and surgical resection of residual primary tumor following completion of neoadjuvant chemotherapy;
- **6.1.4** Tumor size ≥2cm, measured on imaging or estimated by physical exam;
- **6.1.5** No contraindications for primary chemotherapy;
- **6.1.6** Planned definitive breast surgery (mastectomy or lumpectomy/breast conservation) following completion of neoadjuvant therapy;
- **6.1.7** Age 18 years or older;
- **6.1.8** ECOG Performance Status ≤ 2 (Karnofsky ≥ 60%; see Appendix II);
- **6.1.9** Adequate organ and marrow function, as defined at participating institutions;
- **6.1.10** If female, postmenopausal for a minimum of one year, OR surgically sterile, OR not pregnant, confirmed by a pregnancy test as per institutional SOC, and willing to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation;
- **6.1.11** Able to understand and willing to sign a written informed consent document and a HIPAA authorization in accordance with institutional guidelines;

6.2 Exclusion Criteria

- **6.2.1** Previous treatment (chemotherapy, radiation, or surgery) to involved breast;
- **6.2.2** Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements;
- **6.2.3** Medically unstable;
- **6.2.4** Under age 18;
- **6.2.5** Pregnant or nursing;
- **6.2.6** Previous malignancy, other than basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix, from which the patient has been disease free for less than 5 years;
- **6.2.7** Neoadjuvant hormonal therapy will not be allowed.

6.3 Evaluability for Primary Aim

A participant will not be considered as evaluable for the primary aim if:

- **6.3.1** Participant who does not receive the baseline and/or mid-point DOSI scan;
- **6.3.2** Baseline scan and/or mid-point DOSI scan does not meet Quality Control (QC) criteria for imaging quality;
- **6.3.3** Participant does not undergo surgery post NAC and/or final pathology data is not available for analyses.

6.4 Recruitment and Screening

No optics trials compete with this trial and would be the first of its kind. ACRIN 6657 have similar participant population and these patients are anticipated to also enroll in this study. The investigative team at each participating site includes the medical oncologist, surgeon, imaging scientist trained to use DOSI instrument, and radiologist. Potential participants will be referred by the surgical oncologist and/or medical oncologist.

ACRIN will develop a trial communications plan that will describe the production of materials to aid participant recruitment. All materials used for participant recruitment will be reviewed and approved by each institution's Institutional Review Board (IRB).

6.5 Inclusion of Women and Minorities

Men are excluded from this study because the number of men with breast cancer is insufficient to provide a statistical basis for assessment of effects in this subpopulation of people with breast cancer. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown below:

Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	2	0	0	2
Not Hispanic or Latino	58	0	0	58
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	60	0	0	**60**
Racial Category				
American Indian or Alaskan Native	1	0	0	1
Asian	1	0	0	1
Black or African American	4	0	0	4
Native Hawaiian or other Pacific Islander	1	0	0	1
White	52	0	0	52
More than one race	1	0	0	1
Unknown	0	0	0	0
Racial Category: Total of all subjects	60	0	0	**60**

7.0 SITE SELECTION

7.1 Institution Requirements

The limited participating institutions for this study are NTR approved institutions that meet qualifications for participating in this study and are ACRIN-participating institutions. Each institution must complete a Protocol Specific Application (PSA) (Appendix 2; available online at www.acrin.org/6691_protocol.aspx) and have the DOSI device approved prior to the institution participating in the study (Appendix 2). Detailed information for DOSI Qualification Procedures and its application to become qualified, as well as the PSA can be accessed at www.acrin.org/6691_protocol.aspx. All regulatory documentation must be submitted to ACRIN Headquarters (via fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department)

7.2 IRB Approval and Informed Consent Form

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). The ICF is included in this protocol as Appendix 1. The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and a copy of the IRB-approved, site-specific ICF must be delivered to the trial monitor to review the approved form and to keep on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance Department) prior to registering the first participant.

7.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 60 participants. During the first six months, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment,

technical, and communication barriers. In particular, starting approximately one month after a site is approved to begin participant enrollment, the site's actual accrual will be compared to the average monthly accrual potential described in their PSA. If a site's actual accrual falls below 60% of what is reported in the PSA, ACRIN will determine a follow-up action plan to identify site accrual barriers and develop strategies to support the site in meeting accrual goals.

The ACRIN Steering Committee regularly reviews the overall trial accrual and may request information about a trial's accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ACRIN Data Safety and Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

8.0 DATA MANAGEMENT/ONLINE REGISTRATION

8.1 General

8.1.1 The ACRIN web address is www.acrin.org.

8.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.

8.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-registration. A DMC contact list is located on the ACRIN web site for each protocol.

8.2 Clinical Data Submission

8.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

8.2.2 The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as

open/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

8.2.3 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.

8.2.4 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

8.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

8.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

8.4 Electronic Data Management

8.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the DMC. The logic checks

performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC research associate. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.

8.4.2 If checks at DMC or BC detect missing or problematic data, the DMC personnel assigned to the protocol sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC updates the participant's data submission calendar with the due date for the site RA or investigator's response.

8.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool.

8.6 Data Quality Assurance

8.6.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

8.6.2 A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) department, until the problem has been resolved. If the BDMC, along with the PDRC, cannot find a resolution

to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

8.6.3 In addition, the ACRIN QA Monitor will review case report forms and source documents at several different time points: after first few participants enrolled and during the conduct of the trial, including staff changes at the participating sites. In addition, the QA Monitor will review the initial and annual regulatory documents and any revised regulatory documents. This monitoring process ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the case report forms.

9.0 STUDY PROCEDURES

9.1 Eligibility and Registration Visit

Initial assessment to determine eligibility will occur prior to the initiation of chemotherapy and will comprise of the following:

- A signed informed consent;
- Confirmation of eligibility as outlined in Section 6.0;
- Review of medical history;
- Physical examination;
- Pregnancy test, as per institutional standard of care;
- Review the standard clinical test results, as outlined in Section 6.1.7;
- Review of pathology report confirming diagnosis from initial biopsy;
- Review CT, mammogram, MRI, and/or any other scans of chest if available;
- Review any other scans performed for evaluation, e.g. x-rays, if indicated.

9.2 Visit 1 Baseline

The baseline visit (DOSI 1) will occur at least two weeks post biopsy and within two weeks of the first chemotherapy cycle. DOSI may be performed on the same day as chemotherapy. The visit will comprise the following:

- DOSI
- Review of standard of care imaging (e.g. MRIs, mammograms, ultrasounds, etc)
- Adverse event assessment

9.3 Visit 2 Early-Therapy

The early-therapy (DOSI 2) visit will occur 5-10 days after the initiation of the first cycle of chemotherapy. The visit will comprise the following:

- DOSI
- Review of standard of care imaging (e.g. MRIs, mammograms, ultrasounds, etc)
- Adverse event assessment

9.4 Visit 3 Mid-Therapy

Mid-therapy DOSI (DOSI-3) must be performed halfway through the therapy protocol and at least 5 days after completion of the last chemotherapy prior to the mid-point, and prior to the first chemotherapy cycle after the mid-point or change in chemotherapy regimen. The visit will comprise the following:

- DOSI
- Review of standard of care imaging (e.g. MRIs, mammograms, ultrasounds, etc)
- Adverse event assessment

9.5 Visit 4 Post-Therapy

The post-therapy (DOSI 4) visit must be performed after completion of last cycle of chemotherapy and prior to surgery. The visit will comprise the following:

- DOSI
- Review of standard of care imaging (e.g. MRIs, mammograms, ultrasounds, etc)

9.6 Study Procedures Table

Study Procedure	Registration Visit	VISIT 1: Baseline Performed at least 2 weeks post biopsy and less than two weeks prior to the first chemotherapy cycle	VISIT 2: Early-therapy 5-10 days after the initiation of first cycle of chemotherapy	VISIT 3: Mid-therapy Mid-therapy DOSI (DOSI-3) must be performed halfway through the therapy protocol and at least five (5) days after completion of the last chemotherapy prior to the mid-point, and prior to the first chemotherapy cycle after the mid-point or change in chemotherapy regimen.	VISIT 4: Post-therapy After completion of chemotherapy and prior to surgery	Post-surgery
Informed Consent Form	x					
Screening/Eligibility Review	x					
Physical Examination	x					
Pregnancy test, as per institutional SOC	x					
Medical History	x					
Review of Clinical Test Results	x					
Review of pathology report from initial biopsy	x					
Review of pathology report from surgery						x
Review of diagnostic imaging (e.g., MRI, mammography, ultrasound imaging, etc)	x					
Review of any prognostic imaging (e.g., MRI, mammography, ultrasound imaging, etc)		x	x	x	x	
Medical Record Review	x					
ACRIN Web Registration	x					
Study Imaging: DOSI		x	x	x	x	
Adverse Event Assessment		x	x	x	x	

10.0 IMAGING PROTOCOL

The protocol required images must be in DICOM format on CD/DVD-ROM or submitted via the internet using secure File Transfer Protocol (FTP), and transmitted along with an Imaging Transmittal Worksheet (ITW) which can be found on the ACRIN 6691 web site

(www.acrin.org/6691_protocol.aspx). The required images must be submitted to ACR Imaging Core Lab. ACRIN can provide electronic image submission and anonymity utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the Image Management Center (IMC) via email at Triad-Support@phila.acr.org or via phone: 215-940-8820.

10.1 If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using FTP, or CD-ROM where appropriate, for purposes of secondary review.

10.1.1 Removal of Confidential Participant Information: The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the image are transferred.

This involves **replacing** the following:

- Participant Name tag with the ACRIN Institution ID or number
- Participant ID tag with the ACRIN case number, and
- Other Participant ID tag with ACRIN Study Number.

10.1.2 FTP Transfer: Digitally generated image files in DICOM v3.0 format can be transmitted to the ACRIN IMC via FTP directly to the image archive. This can be performed using a customized software program or by using TRIAD software available from ACRIN. An Imaging Transmittal Worksheet (ITW) must be faxed at the time images are transmitted. Contact the ACRIN IMC for additional details at Triad-Support@phila.acr.org

10.1.3 Please fax the ITW to:
ACRIN Core Lab at (215) 923-1737, ATTN: ACRIN 6691 Imaging Specialist

10.1.4 In the event that the transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN IMC for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

10.1.5 Images and the ITW may be mailed to:

American College of Radiology Clinical Research Center
ACR Imaging Core Laboratory
Attn: ACRIN 6691
1818 Market Street 16th floor
Philadelphia, PA 19103

11.0 STUDY SPECIFIC RISKS/ADVERSE EVENT REPORTING

Prompt reporting of adverse events (AEs) is the responsibility of each site principal investigator (site PI). Anyone uncertain about whether a particular event should be reported should contact the American College of Radiology (ACR) Headquarters at (215)574-3150 and ask for the ACRIN AE Coordinator for further assistance.

Adverse events (AEs) as defined in the tables below and all serious adverse events (SAEs) will be reported to the Cancer Imaging Program (CIP) via the Adverse Event Expedited Reporting System (AdEERS) application as directed in this section.

For optical imaging, since no contrast or other drug is administered; adverse event monitoring will be during the optical study, and at the completion of the optical study; a total time period of 1-2 hours or less per optical imaging session including set-up and completion of imaging.

AdEERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is broadly intended to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. Adverse Event Reporting must follow the guidelines below. The latest version of the NCI/CTEP Adverse Event Reporting Requirements document, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf provides additional details, and may be consulted as a reference, but **does not supersede AE reporting as specified in this protocol.**

The electronic-AdEERS AE system is to be used for all 'expedited reporting' events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. Expedited AE data is to be re-submitted via the electronic AdEERS system as soon as is possible in cases where temporary e-AdEERS unavailability has necessitated manual capture and submission.

11.1 General Definitions

11.1.1 Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event (SAE)
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

11.1.2 Life-Threatening Adverse Event

A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

11.1.3 Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participants offspring)

11.1.4 Adverse Event Expedited Reporting System (AdEERS)

AdEERS is a web-based system created by NCI for electronic submission of SERIOUS and/or UNEXPECTED AE reports & is to be used in this study.

11.2 AE Reporting Requirements

The characteristics of an observed AE will determine whether the event requires expedited (via electronic-AdEERS) reporting **in addition** to routine reporting. Please see sections 11.5-11.8 for study specific reporting requirements. Attributions are in terms of the study related imaging procedures.

11.3 Adverse Event Characteristics

Expected Adverse Event: An expected AE is an event that is listed in the protocol or the Investigator's Brochure.

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the protocol or the Investigator's Brochure.

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure

Grade: Grade denotes the **severity** of the AE. An AE is graded using the following categories:

- **Mild**
- **Moderate**
- **Severe**
- **Life-threatening or disabling**
- **Fatal**

NOTE: Severity is graded on a CTCAE based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness," which is an overall assessment [See SAE above] that determines reporting requirements.

11.4 CTCAE term (AE description and grade)

The descriptions and grading scales found in the most current release version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the most current CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).]

11.5 Expectedness

AEs can be 'Unexpected' or 'Expected' see above for characteristics.

11.5.1 Expected Adverse Events Associated With DOSI

The optical scan is not expected to cause any pain, burning, or discomfort during or after the exam. There may be risks, however, that are currently unforeseeable. During all measurements, the laser will be turned on only when needed. Although not required for safety, subjects may wear protective eye goggles if requested. The optical power launched into the tissue averages 20mW (comparable to halogen-bulb household flashlights).

11.5.2 Risk of Device-related Events:

- Device failure and/or malfunction;
- Calibration, calculation, or targeting error.

11.6 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use electronic AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in Table A below.

NOTE: 24-Hour Notification

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade and attribution.

11.6.1 24 Hour Telephone Reporting Instructions

Any AE/SAEs that require 24-hour notification as outlined in the study-specific protocol, please call the following numbers to report the event:

1. **CIP– SAE Reporting Line: (301)897-1704**
   - The CIP-SAE reporting line is staffed Monday through Friday from 7:30am – 7:30pm ET (Eastern Time).
   - AE/SAEs may be reported via voicemail during off hours.
   - A TRI contact for AE/SAE reporting will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:

- Name of person reporting the AE/SAE and telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the adverse event
- Site principal investigator's assignment of the attribution of the adverse event (do not delay initial report if not available)

11.6.2 ACRIN–AE/SAE Reporting Line: (215)717-2763

- The ACRIN–AE/SAE reporting line is monitored by the ACRIN AE Coordinator: Monday through Friday from 8:30am – 4:30pm ET.
- AE/SAEs may be reported via voicemail during off hours.
- The ACRIN AE Coordinator will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:

- Name of person reporting the AE/SAE, telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator's name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the adverse event
- Site principal investigator's assignment of the attribution of the adverse event (do not delay initial report if not available)

IMPORTANT: After the 24 hour contact to CIP and ACRIN-AE/SAE reporting lines, an electronic Adverse Event Expedited Report (AdEERS) must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

11.6.3 Submitting an AdEERS Report: Electronic Submission

Any AE/SAEs requiring expedited reporting must be submitted via the AdEERS web application. Please find the AdEERS application on the NCI/CTEP web page at: http://ctep.cancer.gov/reporting/adeers.html.

11.6.4 Submitting an AdEERS Report: System Unavailable

In the rare event that Electronic AdEERS [internet] access is lost, an AE report may be submitted using the following process:

1. Sites should download reporting forms in advance and store them locally for access in the event of internet unavailability. They can be found at: http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers
2. Site chooses Single or Multiple Agent template as appropriate.
3. Site completes appropriate sections of the SAE submission form.
   NOTE: For 24-hour notification, site follows up with a faxed SAE submission within 5 business days.
4. Site faxes SAE submission form and any additional information (source documents) necessary for thorough review of the event(s) along with the SAE submission form to 301-897-7402, attention CIP SAE Team. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure (Tel. 301-897-1704), and should be contacted to confirm receipt of materials sent during any period of AdEERS unavailability, or to provide guidance with the process as appropriate.
5. Site follows up with an email to CIPSAEReporting@tech-res.com notifying the SAE Team that an SAE form and additional information (if available) has been faxed.
6. Once AdEERS access is restored, an AE report submitted by the backup process must be entered electronically into AdEERS by the original submitter at the site.

11.7 Expedited & Routine Reporting Guidelines

TABLE A
All Phases
AdEERS reporting requirements for adverse events occurring within 30 days the last study related procedure

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
		Unexpected			Unexpected		Expected					
	Unexpected and Expected	with Hospital-ization	without Hospital-ization	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected	Expected	Un-expected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	**10 Calendar Days.** **Routine Reporting also applies.**	Expedited Report Not Required. **Routine Reporting applies**	Expedited Report Not Required. **Routine Reporting applies.**	Expedited Report Not Required. **Routine Reporting applies.**	**24-Hour; 5 Calendar Days.** **Routine Reporting also applies.**	**10 Calendar Days.** **Routine Reporting also applies.**	**24-Hour; 5 Calendar Days.** **Routine Reporting also applies.**	**10 Calendar Days.** **Routine Reporting also applies.**

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.
Attributions are in terms of the study related imaging procedures (including contrast agent and IV administration).

11.8 AE Reporting Timelines Defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
- "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Routine Reporting - Completion of an adverse event case report form.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

11.9 Routine Adverse Event Reporting

The following adverse events **must** be reported in routine study data submissions (i.e. ACRIN AE case report form).

- Grade 3 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 11.7 Table A for AdEERS reporting requirements].
- Grade 4 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 11.7 Table A for AdEERS reporting requirements].
- Grade 5 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 11.7 Table A for AdEERS reporting requirements].

AEs reported through AdEERS must also be reported in routine study data submissions.

12.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB) for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study.

The investigator will provide ACRIN with the institution's federal wide assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved ICF. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

All study participants in this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for an ICF template). The ICF will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. Any revisions to the ICF at any time during the trial will need to be submitted to the IRB for approval and submission to ACRIN PDRC.

13.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN Conflict of Interest policies and applicable federal, state, and local laws and regulations.

14.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ACRIN, Bruce Tromberg, PhD, and the ACRIN Publication Committee. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the ACRIN Publication Policy (available online at www.acrin.org/PublicationsPolicy.aspx).

15.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating sites' study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

15.1 Monitoring

Monitoring ensures data integrity and quality, as well as that the rights, safety, and well-being of the participants are protected. Monitoring also makes certain that the trial is in compliance with the currently approved protocol/amendments, with GCP and applicable regulatory requirements. It ensures the reported trial data are accurate, complete, and verifiable from source documents. Institutional monitoring will be implemented at several different time points during the conduct of the study. Case report forms (CRFs) and source documents of study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents will also be monitored.

15.2 Audits

All participating institutions with study participants will be audited. The timing of initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site enrollment), the number of evaluable participants at an individual site, the status of the protocol and pending amendments, and status of the site monitoring.

Generally, audits will be conducted after the number of evaluable participants reaches 30% of targeted accrual, either study-wide and/or at the site level. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate an immediate audit visit. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited which may affect the conduct of the trial. Additionally, site-specific circumstances may prompt an audit visit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. Audits can be conducted more frequently at the discretion of the protocol team. The audits will be conducted per procedures established by the NCI/CIP. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. CRFs and study-related source documents of study participants enrolled at each site will be audited. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN and NCI/CIP.

IRB procedures, approvals, and ICFs may also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org/pdrc.aspx.

To help sites prepare for monitoring and audit visits and to assure that the investigator and the research staff maintain appropriate study-related documents, ACRIN Headquarters will offer training to any participating sites. The training will include all aspects of data collection and special instructions to obtain, file, and maintain the various source documents for verification of submitted trial data. Please refer to the study-specific protocol audit guidelines for details.

15.3 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical examination alluding to a condition, but no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

15.4 Case Report Forms (CRFs)

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case, "N/A" must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation if signed by the Investigator. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

15.5 Institutional Review Board

Sites must obtain initial local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

16.0 STATISTICAL CONSIDERATIONS

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16.4 Reporting Guidelines

Routine reports for this protocol will be included in the ACRIN Biostatistics Center Mid-Year and Year End Updates and will be provided to oversight bodies, including DSMC for review during each of its twice-yearly meeting.

Routine reports will include:

- Accrual and participant characteristics
- Timeliness and completeness, eligibility and protocol compliance, and outcome data
- All reported adverse events

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APPENDIX I: INFORMED CONSENT FORM TEMPLATE

ACRIN 6691

Monitoring and Predicting Breast Cancer Neoadjuvant Chemotherapy Response Using Diffuse Optical Spectroscopic Imaging (DOSI)

[Note: The American College of Radiology Imaging Network (ACRIN) does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); that is the responsibility of local Institutional Review Boards (IRBs). Local IRBs may choose to combine the authorization elements in the informed consent. Information on ACRIN's HIPAA policy, as well as a template for HIPAA authorization, can be found at www.acrin.org.]

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet "Taking Part in Clinical Trials: What Cancer Patients Need to Know" is available from your treating doctor.

You are being asked to be in this study because you have breast cancer. We are going to evaluate the usefulness of imaging using an experimental device to determine the effectiveness of the chemotherapy in treating breast cancer.

WHY IS THIS STUDY BEING DONE?

This research study is being done to test the effectiveness of an experimental imaging technology known as Diffuse Optical Spectroscopy Imaging (DOSI) in predicting the success of chemotherapy treatment (shrinkage of tumor). Experimental imaging devices are being developed to monitor and predict breast cancer response to neoadjuvant chemotherapy, both prior to and as early as possible during the course of treatment. It will be compared to any other imaging during your treatment.

DOSI is relatively simple to perform and interpret compared to other imaging technologies. Because of its size and portability, DOSI can potentially create new opportunities for patients to receive personalized treatment, and for doctors to gain new insight into response mechanisms. A practical advantage of DOSI is that it can be administered frequently at the bedside in unconventional settings such a doctor's office or infusion center. You will not have a direct benefit from being in this study, but will be contributing to the knowledge that may benefit future breast cancer patients.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

60 women will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Screening Visit

If you choose to take part in the study, you will be asked to come to the medical center at least two weeks after your biopsy to determine whether you meet the study entrance requirements. At this time, your medical history will be taken, you will have a physical exam, and your vital signs (temperature, blood pressure, heart rate and blood oxygen level) may be recorded. You may also be asked to take a pregnancy test. You are not allowed to be pregnant or become pregnant while

on the study. Some of this information may be taken from your medical records. The results from laboratory tests previously performed will be reviewed. The tissue from your initial biopsy will be evaluated by the pathologist at your institution, as per standard of care.

If you choose to take part in the study, four (4) DOSI scans will be performed. Each DOSI scans will take about 30 minutes/session. If participants receive additional DOSI measurements, this data will be collected.

First Imaging Session*: *Baseline DOSI
The first DOSI scans will take place at least two weeks post biopsy and less than two weeks prior to initiation of therapy protocol. This DOSI scan must be performed before you start your chemotherapy and may take place on the same day as your first chemotherapy session.

Second Imaging Session: Early-Therapy DOSI
The second imaging session will take place 5 to 10 days after you start chemotherapy.

Third Imaging Session: Mid-Therapy DOSI
The third imaging session will take place midway through your planned course of chemotherapy.

Fourth Imaging Session: Post-Therapy DOSI
The fourth imaging session will take place after you finish your planned course of chemotherapy and before your surgery. This will be the last imaging session.

Surgery and tumor tissue collection
After the last DOSI session, you will be scheduled to have surgery to remove any remaining tumor that is left after chemotherapy. This surgery is the standard of care for the treatment of your disease and is not a part of the imaging research.

HOW LONG WILL I BE IN THE STUDY?
Your participation in this study will last throughout the course of your chemotherapy treatment and is predicted to take up to 9 months, depending upon the length of chemotherapy treatment used in your center. Your direct participation will consist of a screening visit and four imaging sessions (just before you start chemotherapy treatments, one week after you start chemotherapy treatments, and halfway through your entire planned course of chemotherapy treatments, and after chemotherapy). The imaging sessions have a total of four DOSI scans. Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent. The reasons might include:

- The study doctor thinks it necessary for your health or safety;
- You have not followed study instructions;
- The sponsor has stopped the study;
- Administrative reasons require your withdrawal.

WHAT ARE THE RISKS OF THE STUDY?
Risks of DOSI
There are no known side effects from the use of DOSI.

WILL I KNOW MY RESULTS?
The final results from this research study may be shared with your treating doctor only after the study is completed. The treating doctors will have access only to standard of care imaging data

during the study. As DOSI remains experimental, these early imaging results are not yet fully understood. The experimental imaging results should not and will not change your treatment course and will not be part of the medical record.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
This is not a treatment study and you are not expected to receive any direct medical benefits from your participation in this imaging study. The information learned from this study may lead to a better identification of treatment response in the future for patients with breast cancer.

WHAT OTHER OPTIONS ARE THERE?
This is not a treatment study and you may choose not to participate in this study. You will receive the current standard of care for the treatment of breast cancer and your treating doctor can tell you more about the possible benefits of different available treatments.

WHAT ABOUT CONFIDENTIALITY?
Every attempt will be made by the study doctor to keep all the information collected in this study strictly confidential, including your personal information. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN). All data sent to ACRIN over the Internet will be coded so that other people cannot read it. Your personal information may be disclosed if required by law.

Authorized representatives of ACRIN, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the local Institutional Review Board (IRB), the Statistical Center at Brown University, and other groups or organizations that have a role in this study will have access to and may copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your images from the breast examination and some physical information about you (such as your age, gender, and possibly symptoms), and the results of any biopsies and pathology analysis of tissue from surgery will be sent to an electronic database to be kept permanently on file at ACR Clinical Research Center in Philadelphia, PA, National Institutes of Health, and NCI in Bethesda, MD for use in future research. Your name and other information that could be used to identify you personally will not be included.

WHAT ARE THE COSTS?
The National Cancer Institute (NCI) will provide all the DOSI studies free of charge for this study.

There will be no charges to you for any visits or tests related solely to the imaging research study. You or your insurance will be billed for any treatments or procedures that are a part of the standard of care for your cancer (these are the costs that you would have whether or not you participated in this research study).

WHAT IS THE PAYMENT FOR PARTICIPATION

The National Cancer Institute (NCI) does not pay subjects to participate in its research studies. However, NCI has authorized reimbursement of reasonable travel expenses, parking and meals associated with participation in this study.

WHAT IS THE COMPENSATION FOR INJURY

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to leave the study, please contact the study doctor so that he/ she can tell you how to stop the study safely

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For additional information about your health, you may contact:

_____

_____

Name Telephone Number

For additional information about this study, you may contact:

_____

_____

Name Telephone Number

For information about your rights as a research subject, you may contact:
(*OHRP suggests that this person not be the investigator or anyone else directly involved with the research)*

_____

_____

Name Telephone Number

For additional information in the case of injury or illness related to research, you may contact:

_____

_____

Name Telephone Number

WHERE CAN I GET MORE INFORMATION?
You may call the NCI's Cancer Information Service at 1-800-4- CANCER (1-800-422-6237) or TTY:1-800-332-8615.

Visit the NCI's Web sites for comprehensive clinical trials information http://cancertrials.nci.nih.gov or the American College of Radiology Imaging Network's website **www.acrin.org.**

For more information on DOSI scans you can go to ACRIN's Website at: http://www.acrin.org/PATIENTS/ABOUTXRAYSANDSCANS/tabid/135/Default.aspx .You or your treating doctor can print a description of DOSI scans from this website.

SIGNATURE
I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion. I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Participant (or Legal Representative) Signature Date

APPENDIX II: KARNOFSKY AND ECOG PERFORMANCE CRITERIA

KARNOFSKY ACTIVITY	SCORE %	ECOG GRADE	ECOG ACTIVITY
Normal, no complaints on all predisease activities	100		Fully active, able to carry
Normal, only minor signs/symptoms	90	0	without restrictions
Normal activity, but requires effort	80		No physically strenuous activity, but ambulatory
		1	and able to carry out light
Unable to do active work, but able to care for self	70		or sedentary work (eg., office work, light house work
Able to care for most needs, requires occasional help	60		Ambulatory/capable of all self-care, unable to
		2	perform any work activities Up and about more than
Requires frequent medical help and considerable assistance	50		50% of waking hours
Disabled, needs special assistance	40		Capable of only limited care and and self-care, confined to
		3	bed or chair for more than 50% of waking hours.
Severely disabled, needs hospitalization, death not imminent	30		
Very sick, hospitalized, active support needed	20		Completely disabled,
		4	totally confined to bed or chair.
Cannot carry on any self-care.	10		
Dead	0	5	

APPENDIX III: SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

ACRIN 6691

Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN 6691 Protocol Web page (**www.acrin.org/6691_protocol.aspx**). Types of materials posted include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, FDA Form 1572, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Image Transmittal Worksheet, imaging parameter charts, and scanning and image qualification instructions);
- Recruitment and education materials;
- Regulatory resources;
- Participating site list

For more information related to the trial, contact the ACRIN 6691 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.