

# Quality control and assurance for validation of DOS/I measurements

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## ABSTRACT

Ongoing multi-center clinical trials are crucial for Biophotonics to gain acceptance in medical imaging. In these trials, quality control (QC) and assurance (QA) are key to success and provide “data insurance”. Quality control and assurance deal with standardization, validation, and compliance of procedures, materials and instrumentation. Specifically, QC/QA involves systematic assessment of testing materials, instrumentation performance, standard operating procedures, data logging, analysis, and reporting. QC and QA are important for FDA accreditation and acceptance by the clinical community. Our Biophotonics research in the Network for Translational Research in Optical Imaging (NTROI) program for breast cancer characterization focuses on QA/QC issues primarily related to the broadband Diffuse Optical Spectroscopy and Imaging (DOS/I) instrumentation, because this is an emerging technology with limited standardized QC/QA in place. In the multi-center trial environment, we implement QA/QC procedures: 1. Standardize and validate calibration standards and procedures. (DOS/I technology requires both frequency domain and spectral calibration procedures using tissue simulating phantoms and reflectance standards, respectively.) 2. Standardize and validate data acquisition, processing and visualization (optimize instrument software-EZDOS; centralize data processing) 3. Monitor, catalog and maintain instrument performance (document performance; modularize maintenance; integrate new technology) 4. Standardize and coordinate trial data entry (from individual sites) into centralized database 5. Monitor, audit and communicate all research procedures (database, teleconferences, training sessions) between participants ensuring “calibration”. This manuscript describes our ongoing efforts, successes and challenges implementing these strategies.

**Keywords:** quality assurance, quality control, validation, optical imaging, breast cancer, biophotonics

## 1. INTRODUCTION

Optical imaging of tissue, in particular with regard to detection and characterization of breast cancer, has made enormous strides in recent years. For example, a recent study from our laboratory has succeeded in identifying optical biomarkers that can discriminate benign from malignant lesions in breast cancer.<sup>1</sup> Notwithstanding these advances the clinical acceptance of the technology has lagged. One reason for the phase lag of clinical implementation has been the general absence of rigorous quality control (QC) and assurance (QA) measures documenting and validating the engineering studies and pilot clinical trials. The success of any multi-center clinical trial depends upon the coherent collection and analysis of quality data. Quality control and assurance are key to success and provide “data insurance”. Quality control and assurance deal with standardization, validation, and compliance of procedures, materials and instrumentation. Specifically, QC/QA involves systematic assessment of testing materials, instrumentation performance, standard operating procedures, data logging, analysis, and reporting. Good quality control and assurance makes good and proper scientific sense. Poor quality control and assurance can compromise the study results. With a view to the future, QC and QA are a requirement for FDA application, and are necessary for trial results to gain acceptance by the medical community. In an effort to standardize and validate biophotonics imaging technology we undertook a multi-center breast cancer imaging trial “Breast Cancer Multi-Dimensional Diffuse Optical Imaging” (PI: B. Tromberg) under the auspices of the National Cancer Institute’s Network for Translational Research Optical Imaging (NTROI). The

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multiple sites include: the University of California Irvine (Beckmann Laser Institute; BLI), University of Pennsylvania, Dartmouth College, Massachusetts General Hospital and the University of California San Francisco.

At the Beckman Laser Institute (BLI), we have had pilot clinical trial experience in breast cancer and multi-center study experience for a decade.<sup>2</sup> This experience has sensitized us to QC/QA issues. On occasion operators did not explicitly follow the measurement protocol, forgot to calibrate, or were unaware that data was of low quality. Even within our group at BLI, we found that measurement technicians were not always calibrated with each other in their measurement techniques during long term longitudinal monitoring studies, resulting in increased variance and anomalous data points. These problematic results appeared despite extensive on-site training. Other research groups have reported similar experiences.<sup>3</sup>

All research studies, clinical or otherwise, should have a data quality control and assurance plan in place *before* the acquisition of data. The terms quality control and quality assurance for our purposes are defined and distinguished as follows: *quality control* (QC) is the verification that data is generated, collected, handled, analyzed and reported according to protocol and standard operating procedures (SOP), whereas *quality assurance* (QA) is the systematic examination of all trial-related activities and documentation<sup>4</sup>. Most studies involving research-grade optical instruments, including ours, are the products of university laboratories that typically stress scientific results and initial translational studies, but have not emphasized standardization. Some research groups engaged in multi-center clinical trials have strongly focused on the necessity of quality control and assurance, and they successfully implemented extensive calibration strategies for their instruments<sup>3, 5</sup>.

We integrated a core unit for implementing and ensuring QC/QA in our NTROI multi-site study. This unit has built all the instrumentation for the multiple sites, constructed and characterized the calibration phantoms, designed and implemented the standardized operating and data acquisition software and performed the operator training for the multiple sites. Unlike other modalities such as MTI or PET, DOS/I (Diffuse Optical Spectroscopy and Imaging) is still in the investigational stage and does not have any recognized standards in place; hence our primary QC/QA effort will be applied to DOS/I. Further, the quality control and assurance core will be heavily integrated with a centralized IT database to ensure that data is properly archived and readily available.

## 2. DOS/I AND THE QC/QA STRATEGY

### 2.1 DOS/I Instrumentation; Laser Breast Scanner (LBS)

The portable, bedside LBS instrumentation that acquires DOS/I data uses both frequency domain<sup>6</sup> and broadband spectral (steady state) technologies<sup>7</sup> (**Figure 1**). Briefly, the frequency domain components measure phase shifts and modulation amplitudes from modulated laser diodes at six discrete wavelengths in the near infrared region across a frequency range of 50 to 500MHz to provide absolute optical properties at the measured wavelengths. The steady state spectroscopy measurements employ a tungsten halogen lamp and record relative spectra in the range of 650 to 1000nm. Both LBS technologies measure patient breasts by means of a handheld optical probe that features a single, fixed distance between source and detector fibers. The handheld probe is moved across the patient's breast in a point scan pattern (grid). LBS initialization, calibration, validation, documentation and archiving to a centralized data base are performed by custom software EZDOS. Clinical data acquisition, display, analysis and archiving are also implemented through EZDOS for centralized archival storage. The measured DOS/I output map provides information about a series of biologically important markers such as hemoglobin, lipid and water and allows for calculation of parameters such as total hemoglobin concentration and tissue oxygen saturation. Further analysis of the data allows for calculation of the diagnostic tissue optical index (TOI)<sup>8</sup> and identification of optical biomarkers at specific points in the imaged map.<sup>9</sup>

### 2.2 QC/QA implementation strategy

To ensure proper QC/QA procedures for DOS/I technology in the NTROI multi-center breast cancer trial, we identified 5 crucial areas of validation and documentation. Specifically, these areas are:

1. Standardize and validate calibration standards and procedures.

2. Standardize and validate data acquisition, processing and visualization
3. Monitor, catalog, and maintain instrument performance
4. Standardize and coordinate database entry of trial data
5. Monitor, audit and communicate all research procedures



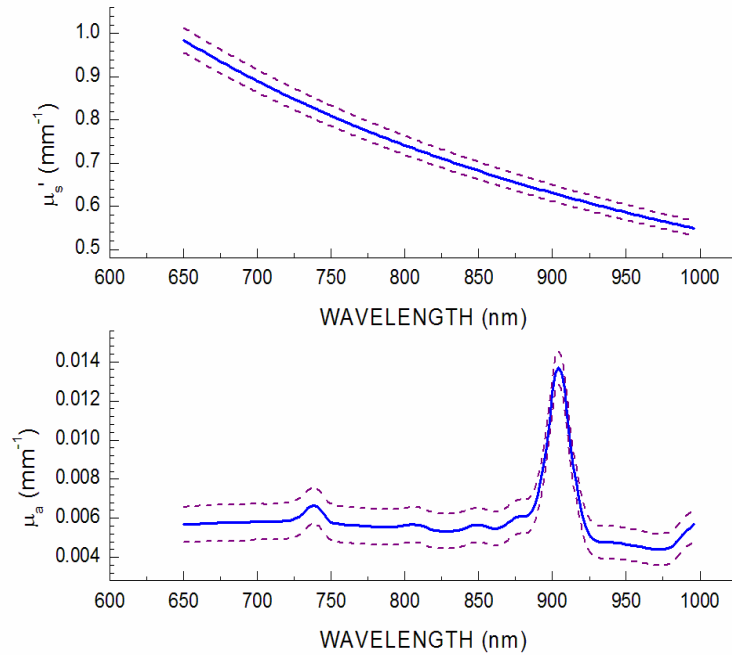
**Figure 1:** The LBS instrumentation is the device shown in the background; the operator is monitoring the output on a computer screen. The handheld probe is on the patient's right breast. The grid of dots on the patient's left breast represents the point scan pattern traced out by the handheld probe. Both the breast with the (suspected) tumor and the healthy breast are measured for comparison purposes. Each measurement point takes a few seconds.

### 3. PRELIMINARY RESULTS

The first aim of our QC/QA strategy is to standardize and validate our calibration standards and procedures for DOS/I in the multi-site breast cancer NTROI trial. Given the clinical nature of our study a number of practical as well as QC/QA issues are evident, especially in regard to calibration phantoms<sup>10</sup>. The calibration phantoms should be constructed of reliable and pure source materials with stable optical properties over time. Utility in the clinical environment limits one to solid phantoms that nonetheless should somewhat mimic breast properties. In the NTROI study, the UC Irvine group constructs the calibration standard and distributes them to all the multi-site centers. Although there is no lack of options for optical phantom recipes, a multi-center clinical trial requires a standardized choice (**Figure 2**). We have recently published online a “how to” manual for the construction of silicone-based phantoms.<sup>11</sup> The online procedures describe not only compositional issues, but also provide detailed instructions for ensuring reproducible phantom construction procedures. These silicone phantoms offer optical properties that are similar to tissue (*e.g.* high scattering and low absorption coefficients). The absorption spectra of these phantoms are not similar to breast tissues; nevertheless they provide a stable and spectrally-flat calibration standard. Initially, two batches of 3 phantoms each were made, with a resulting variance in absorption of 15% and reduced scattering of 3% (**Figure 3**); these characteristics have been maintained in subsequent batches.



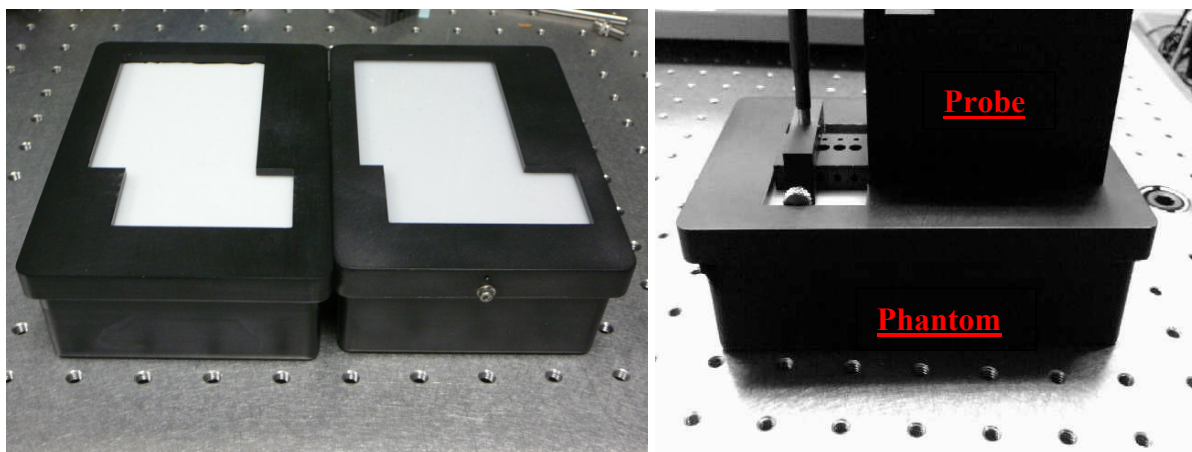
**Figure 2:** Examples of the standardized phantom constructs made of silicone and nigrosin for the NTROI study.



**Figure 3:** Spread in optical properties (reduced scattering and absorption) for the 6 phantoms shown in Figure 2. Variances in the baseline optical properties were 3% for scattering and 15% for absorption.

We have performed additional long term tests of phantom optical stability at several wavelengths (785,810,830,850nm) over time (90 days); as the new phantoms slowly cure (plasticizers) the optical properties (absorption and scattering) gradually drift away from the original values (<10%) to a plateau. Longer term measurements indicate optical stability at the plateau values. We have also performed rigorous initial testing of the phantoms (**Figure 4**) at UC Irvine in an attempt to identify potential sources of measurement error: *i*) multiple measurement technicians (human error) *ii*)

repeated (10X) measurements at each session (measurement variance and probe-phantom coupling issues) *iii*) employing a jig and mask to standardize probe placement on the phantom (positional errors) and *iv*) three different source-detector (S-D) spacings on the measuring probe (explore the homogeneity of phantom optical properties). All of these tests indicate that 10% variability is the target for cross-site reproducibility. These procedures are able to detect changes in phantom optical properties over time, and thus the validity of the calibration standards can be established. The results from these procedures are archived on the centralized database and as the satellite sites generate data during the trial their phantom calibration results will be similarly examined and then archived for a running tally. If after prolonged use (greater than 6 months) the phantom optical properties change significantly, they can be replaced. Two phantoms are measured to provide redundancy and cross validation for the calibration.



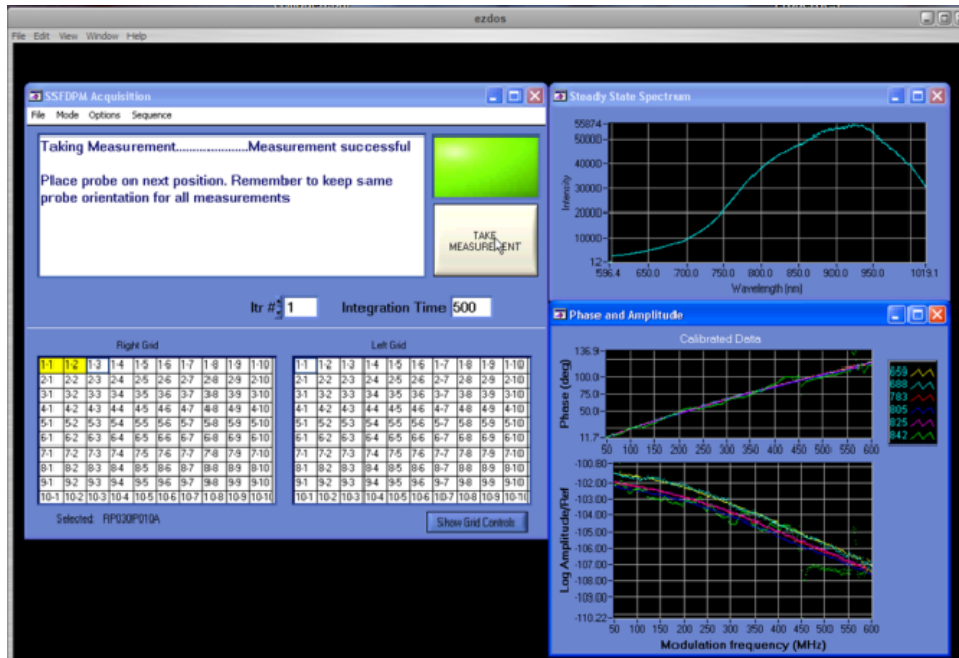
**Figure 4:** The left panel shows two calibration phantoms with examples of a cover mask. The mask is used to position the hand held detector probe in a reproducible manner. The right panel shows the phantom plus mask with the hand held optical probe placed within the mask boundary. The post (source optical fiber) and 3 visible holes at the left side of the photograph correspond to the jig which facilitates reproducible positioning options for changing source-detector (S-D) spacing. For a given S-D spacing a series of 10 measurements is taken and the probe is lifted and repositioned after each individual measurement. This procedure is meant to mimic the placement of the hand held optical probe across the grid of points on the subject’s breast during the trial (see Figure 1).

There are a large number of steps associated with standardizing data acquisition and processing. We have developed the LBS data acquisition software termed EZDOS that performs and checks many of the standardization steps. These steps include: *i*) Consistent acquisition of raw data for phantoms and patients *ii*) Validate data on-the-fly *iii*) alert operators to poor data quality *iv*) centralize data processing to ensure consistency *v*) define and implement standards for data acceptance *vi*) format data for integration into centralized database. To complement the EZ DOS software the UC Irvine group at the BLI sponsored a training session that taught NTROI members the theory and procedures of the DOS/I instrumentation to be used in the multi-center clinical trial. The 2 day training session was “hands on” and followed a technical and procedural manual (developed at BLI) that will be the reference for future research. 22 people attended this event held at the Beckman Laser Institute. The event program and slides are available.<sup>12</sup> The highlight of the event was that attendees were able to witness firsthand an actual clinical measurement performed on a trained patient volunteer. The technical/operation manual is available.<sup>13</sup> Since that early training session, BLI staff have installed LBS instruments at three sites and conducted day long refresher courses.

The EZDOS software is a streamlined, graphical interface that guides the operator through the measurement process with measurement planning, data quality checking and near-real-time data analysis (**Figure 5**). A “traffic light” approach is used to alert the operator when problems arise. As the program initializes the instrument, errors are reported, and the suggested actions are provided to the operator. After initialization, EZDOS steps the user through a power calibration test, for both frequency domain and steady-state light sources, by comparing current optical signals measured from a phantom with optical signals measured from a “factory” test on the same phantom. The operator is then guided through the frequency-domain and spectral calibrations. Once the instrument is calibrated, the operator



generates the measurement spatial grid that defines the area on the breast to be measured. Data checking algorithms alert the user if signals are too low or are noisy. Data analysis is also performed automatically, with about a 3 second delay, thus alerting the operator if points need to be re-measured. A simple demo video of the software is available.<sup>14</sup> *The EZDOS software is important because all DOS/I data will be acquired with EZDOS, and this streamlined graphical interface will reduce operator procedural errors and minimize the collection of poor-quality data.*

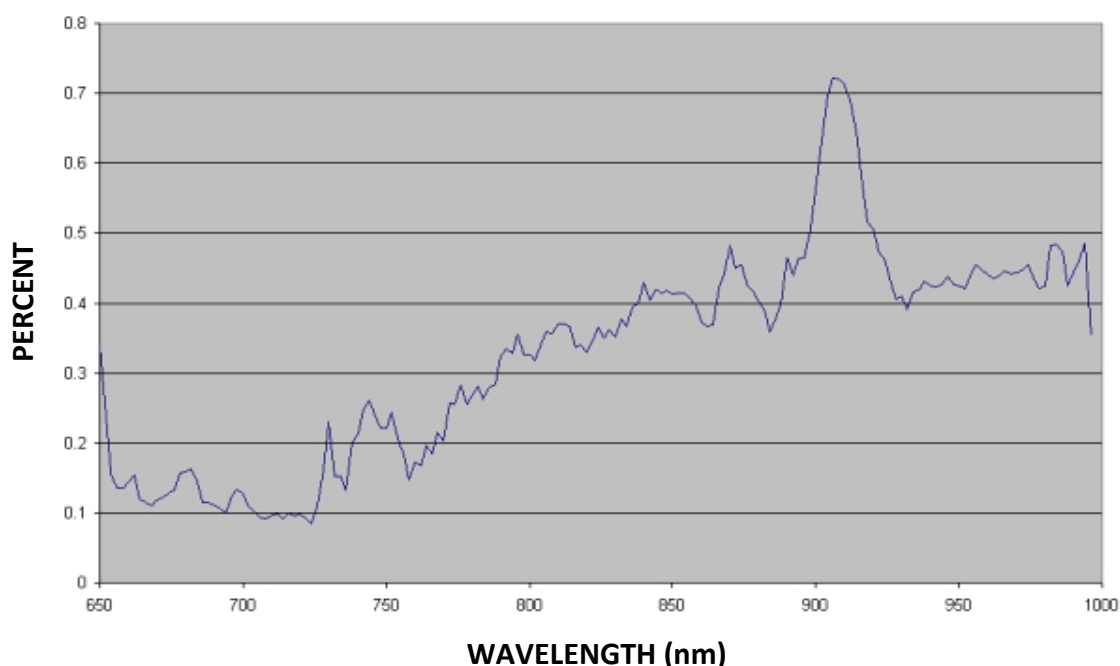


**Figure 5.** Snapshot of the EZDOS software. On the right are the calibrated spectral (above) and frequency domain (below) data. The left side shows the measurement grid (x,y coordinates) for each breast as well as the status of the measurement (upper).

Procedures for monitoring, cataloging and maintaining instrument performance are greatly aided by EZDOS. DOS/I instrument performance must be maintained and validated over the length of the trial. During the construction of all six DOS/I instruments at the BLI, we developed standard tests to ensure that the instrument was working within acceptable bounds. Validation of LBS performance occurs at a variety of points in the EZDOS procedure. For example, at startup the phantoms are measured and if a particular laser diode provides insufficient intensity then the operator is queried about retesting before proceeding further. Another example at initiation concerns the spectral accuracy test (**Figure 6**). A more rigorous test of instrument performance (not part of normal data acquisition) is a 2 hour drift test where the handheld optical probe is attached to a phantom and is left to acquire data undisturbed. We chose 2 hours because the typical measurement is about 1 hour. We can see from Figure 6 that over the 2 hour timeframe, the stability in the absorption spectrum is on average about 0.4%. Although this may seem difficult to achieve for a lamp-based instrument, recall that the DOS/I instrument is a combined frequency-domain and steady-state instrument and the frequency-domain instrument is very stable. Other tests to verify the accuracy and precision of the measurement are under development. The results of the performance metrics are available online.<sup>15</sup>

Periodic application of these tests ensures validation and documentation of instrument performance. Furthermore, multi-site performance of the tests documents and cross-validates instrument performance. By monitoring the archived data from the instrument performance metric technicians are able to detect signal degradation leading to a warning for instrument maintenance. Since the NTROI trial is multi-site the LBS has been designed in a modular fashion facilitating repairs by module exchange.

EZDOS also aids in automated and standardized trial data entry into the centralized database. The hierarchy of the database will permit users to look at raw data, which will be arranged, according first to patient ID and second by measurement date. DOS/I raw data will be processed using separate code developed by UC Irvine, and will then be checked for consistency. Within this context, consistency implies that all model-dependent fits (i.e., FDPM, SS, spectral) are within acceptable tolerance levels. While in the past we have done this subjectively, we will now implement an algorithm that will provide a report to the user that will offer options to retain data integrity. For example, if the 680 nm laser diode is particularly noisy (i.e. an unacceptable  $\chi^2$  merit function) and negatively influences the broadband spectral reconstruction, the data will be reprocessed automatically. Once the processed data has passed inspection, it will automatically be published in the central database and validation will be provided by the QC/QA administrators. In addition, the centralized database will develop simple forms to transfer data from patient charts (i.e. therapy update forms, patient questionnaires) into the database. Simple error checking procedures will be implemented (i.e. identify missing or unphysical values) to reduce data entry errors. The QC/QA administrators will query the database weekly to ensure that the DOS/I data for a particular subject are consistent with the other clinical measurements.



**Figure 6.** Example of results from a 2 hour drift test of instrument (LBS-05) on a phantom (PH-016). Percent is % change from baseline absorption coefficient at time  $t=0$  across the specified wavelength range (650 to 1000nm).

Perhaps one of the most important and often overlooked aspects of quality assurance is the requirement to monitor, audit and communicate all procedures between the participants in the multiple-site trial. As described above all operators at each site receive a 2 day intensive course in the DOS/I theory and operating procedures; with a special emphasis on “hand-on” training with the calibration phantoms, LBS instrumentation, EZDOS software, data acquisition with trained subjects and data analysis. As the trial progresses operators occasionally drift into poor data collection practices or there is turnover in a particular position. Direct and periodic communication via (tele)conference or other means between all the sites is important to keep a high level of QC/QA consistent between the sites. These communications need to be ongoing throughout the length of the trial. It is important that the (tele)conferences include all the involved personnel: clinicians, clinical coordinators, measurement technicians, instrument technicians, database staff, QC/QA administrators and research scientists. To reinforce the lessons of good practice in QC/QA procedures a yearly refresher course for all participants is planned. This conference will also examine the preliminary data acquired to date in the trial and will further offer opportunities for cross validation of the trial data.

#### 4. SUMMARY

After examining the issues of QC/QA and working on their implementation a number of important messages emerge, especially in regard to conducting a clinical trial with an investigational stage technology such as DOS/I. Most importantly, plan and carefully design your QC/QA procedures **before** beginning your trial. Pay attention to quality control issues in regard to materials, instrumentation and training of personnel, but always stay vigilant to quality assurance controls. Test your newly designed QC/QA procedures to verify that they are robust before starting the trial. Throughout the trial stay abreast of quality assurance issues to ensure adherence to standard operating procedures. It is not difficult to drift off course. Periodic review of data archived in the central database, especially in regard to calibration phantoms can provide early indications of technical or procedural difficulties not readily detectable in the clinical data. Rigorously document all procedures and archive both calibration data (phantoms and instrumentation) and clinical data in a central data warehouse for periodic review by QC/QA administrators. It is important to institute periodic review of all data and procedures, especially with regard to cross validation between multiple clinical sites. Each site has the same instrumentation, phantoms and procedural training; cross validation is a good internal monitor of QC/QA. Periodic communication between the QC/QA administrators and the multiple sites, as well as routinely scheduled personnel training sessions for skills updating are of paramount importance in maintaining the highest level of QC/QA.

#### ACKNOWLEDGEMENTS

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