INFORMATION ON DARC: THE DIGITAL ANGIOGRAPHY READING CENTER
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As digital technology became the standard of imaging in ophthalmology, the need to apply it in a clinical trial setting was evident. The result has been the creation of the Digital Angiography Reading Center (DARC), the first fully digital reading center for the evaluation of ophthalmic images; we begin with the screening process and continue through all follow-up visits.

The Digital Angiography Reading Center differs from other reading centers in two important areas. The first is that the personnel who perform the evaluations are physicians who have spent many years in a clinical setting; because of this, they bring experience not available to technicians who are taught to read angiograms without the background in the medical/surgical retina. The second important difference is the experience that we bring to this digital imaging technology that is used for the angiographic studies.
Film-based retinal imaging has been employed since the introduction of fluorescein angiography in 1969. Fluorescein angiographic images were traditionally obtained on conventional fundus cameras using black and white film, with evaluation of the images performed on either negatives or “positive” black and white prints. For over 20 years, stereo viewers and hand-drawn tracings of the fluorescein angiographic studies were the standard for the evaluation and diagnosis of retinal disease.

Since their introduction in the mid-1980’s, digital angiographic systems have gained widespread use in the ophthalmic community and have undergone technical improvements that have advanced their ability to generate high resolution images. Specific advances in digital camera technology and enhancements in computer storage and image evaluation techniques have resulted in the creation of an imaging system certainly equal to the traditional film-based techniques of the past.

Historically, clinical trials have utilized film-based angiographic studies for interpretation by a Reading Center. With few exceptions, this has resulted in eligibility determination and stratification of patients being performed after the individuals have already been enrolled in the trial. In some cases, patients receive study therapy and study medication when they are either angiographically or ophthalmoscopically ineligible for participation in the trial. This is due in part to the fact that angiographic images are often transmitted via conventional mail delivery systems, which delay the evaluation process. In some instances, months can pass before investigators involved in the trial receive input from the Reading Center with respect to eligibility determination and outcome assessment, or even safety information in the course of the trial. In addition, film-based angiography necessitates manual image evaluation and comparison. This process, which has been performed with an exceptionally high level of quality and reproducibility in the past, is a tedious and time-consuming technique. It is also restricted by the need for all readers to be present in a single physical location where the film studies are available for evaluation.
The real-time image quality assessment provided with digital angiography allows photographers to obtain precise images necessary for study protocol examination. A treating physician is able to immediately evaluate these images, determine patient eligibility, and provide patient education directly on a video monitor. An additional advantage includes the ability to digitally archive angiographic studies, thus making them available for future evaluation by both the Study Center and Reading Centers involved in these clinical trials.

Digital angiography allows for rapid communication of images between study sites and the Reading Center. This permits pre-screening and pre-treatment stratification of patients prior to enrollment in a clinical trial.

Computer assisted comparison programs provide for more rapid and more accurate comparisons between imaging studies performed over time. Specifically, digital image analysis provides for the ability to obtain precise area measurements (reported in mm²). The ability to provide these precise measurements as opposed to attempting to fit lesions into pre-determined circles is a clear advantage and allows for more precise follow-up determination of changes in lesion size. Lesions with irregular borders can be precisely mapped and followed and the progression of these lesions outside their original margins can be easily determined by the computer overlay techniques.

Another important aspect of digital imaging is the ability to perform indocyanine green angiography (ICG). ICG examination has clearly been shown to be useful in the diagnosis and evaluation of exudative age-related macular degeneration, in chorioretinal inflammatory diseases, and other retinal pathologies. This imaging technique can only be performed using a digital imaging system and has come to be utilized with increasing frequency in clinical trials of AMD.
To ensure both standardization and high quality of angiographic imaging, all participating study centers use digital imaging systems, computers, and imaging software packages which have been certified by DARC. Image quality and imaging system characteristics are assessed by reviewing images from the system. After the system has been assessed the site is shipped a DARC Test Eye. This test eye is used for measurement calibration of the imaging system from beginning to end of study. Upon receipt of test eye images DARC works with the site to configure the local computer and internet to access DARConline and upload images to the DARC server.

**DATA COLLECTION AND HANDLING**

For clinical trials, the Digital Angiography Reading Center utilizes two independent but interrelated databases. The first database consists of digital images, which are obtained at clinical study sites by DARC certified photographers on DARC certified imaging systems. All study patient angiograms taken at a site are transmitted via the Reading Center secured network to the servers at DARC. All patient information is masked at the sites before being transmitted to DARC where they are stored and archived for purposes of evaluation.

For each clinical trial DARC provides the second custom designed database, which is for the storage and access of data resulting from the evaluation of the angiographic studies. This unique software, based on the Microsoft Access program, provides for a simple but highly secure method of communication between study sites, DARC, corporate Sponsors, and the Data and Safety Committee. DARC staff work closely with Sponsors to design this database to be study-specific.

Protocols are in place to ensure that data provided by the Reading Center are documented, acquired, operated, controlled, released and archived consistently and reliably. These protocols are also designed to ensure the documentation required to control and reliably operate the database system and is readily available for both business operation and regulatory inspection.

The entire database is protected by a unique, multilayered security protocol. Access to the database itself is provided in a password-protected format on an “as needed” basis. For example, each individual study site is only able to enter data and view reports related to patients from their site. Once data is entered and saved, the information converts to a read only format, which prevents alterations in the database. A “deletion/change” protocol exists to allow for modifications of the database. This protocol automatically backs-up all of the original data into a separate database that can be accessed by regulatory agencies if needed to confirm the validity of the system. Corporate sponsors and
the Data and Safety Committee can view all aspects of the database but have no ability to enter data of any kind. This also ensures the integrity of the system.

Additional software features allow for online customized reports of data to be generated and accessed by the corporate sponsors on a continuous basis.

**SAMPLE PROTOCOL FOR CLINICAL TRIAL**

- Photographers and imaging systems at sites which will participate in the clinical trial are certified by DARC
- DARC protocol angiographic data is obtained and stored on the hard drive of the participating clinical center.
- The angiographic file is copied and masked using the patient study ID number. All reference to the individual patient’s information is now eliminated from this file.
- The clinical study site now logs onto the DARC server using DARC’s secure web-based interface. At this point the site can now access the image transfer and imaging databases. to send study patient images and enter pertinent online forms.
- The image files are received by the Reading Center server and downloaded in a format available for evaluation.
- Two readers evaluate angiograms; once a consensus is reached the completed evaluation information is recorded in the specialty-designed database, This analysis is done by trained physician readers either at the Reading Center or at a remote Reading Center location.
- Utilizing the DARConline Internet connection and patient information database, the study sites are able to access information required under the study protocol to be entered on the case report forms as soon as it is entered on the system.
- All screenings take place on a “24 hour basis.” In the rare event where the investigator requires a “same-day” evaluation, the investigator contacts the Reading Center to notify the personnel that an angiogram will be arriving that must be screened immediately. Readers will then utilize either the local area network, or remote access to provide the investigator with a “*stat*” evaluation.
NEW TECHNOLOGIES

DARC continues to utilize new advances in digital technology to expand their roll in clinical trials. Recent advances in clued high resolution digital color imaging, autofluorescent imaging, and Optical Coherence Tomography.

CLINICAL TRIALS EXPERIENCE

DARC has been involved in multiple phases of ophthalmic clinical research for the past 7 years. DARC has worked with sponsors on FDA NDA angiographic data submissions.

The DARC network currently consists of over 200 certified sites, 300 imaging systems and more than 600 certified photographers. DARC has certified the leading types of digital imaging software for use in clinical trials and we continue to expand this list as new software becomes more prevalent.

The DARC staff consists of highly qualified individuals with extensive experience in the fields of clinical research, ophthalmic imaging, and data management. The DARC network at www.DARConline.com is available 24 hours a day 365 days a year to participating sponsors and clinical research sites in over 23 countries worldwide. Our website also provides the opportunity for online tutorials and exams for investigator certification, and tutorials for angiographic protocols and imaging techniques.
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