**Introduction**

When a clinic decides to participate in a clinical trial requiring the submission of digital retinal images it can be a daunting task for photographers. A Reading Center, however, with its dual role of ensuring protocol compliance and assisting the professionals involved with accreditation may help. The Center can help by guiding the photographer through the certification process and ensure continuing adherence to protocol requirements. The following questions are often asked when first entering a clinical trial:

**What is a Reading Center?**

A Reading Center (RC) is a “central laboratory” that specializes in the standardized evaluation of images to determine the presence and severity of various ocular diseases. Diabetic retinopathy and age-related macular degeneration are the diseases most frequently assessed, because they are among the major causes of blindness in the developed world and are drawing more attention in the developing world as cataract and other treatable conditions become better controlled. Reasons for taking and evaluating the images include: clinical trials of potential new therapies, epidemiological studies of the prevalence, incidence and risk factors for eye disease; screening programs to detect persons needing referral to an ophthalmologist and or telemedicine services for patients located far from any ophthalmic services.

**What is Behind Reading Center Requirements for Imaging Equipment and Image Quality?**

There is a fundamental difference between what ophthalmologists and RCs require. The physician almost always examines the patient directly, and uses the images as back-up information for the confirmation of diagnoses and record purposes. The RC does not examine the patient directly, and thus is restricted to whatever information has been captured in the images. Thus, if the images are sub-optimal, the information derived from them may be incomplete or even misleading. Therefore, RCs must have minimum standards of image quality that would convince an auditor that they can plausibly determine ocular disease status with reasonable sensitivity and reliability from the quality of images they are receiving.

**Do Auditors Actually Check to See What Reading Centers are Accepting?**

In multiple clinical trials utilizing different RCs, scientific auditors from the United States FDA, from the corresponding European Community agency, and from other national regulatory authorities have indeed required
submission of some or all of the images obtained in drug trials for their close inspection. As they consider applications for drug approval, regulatory agencies want to look at the images themselves, so that they can form their own conclusions about the safety and efficacy of experimental treatments. Regulators also want to check the gradings performed by RCs against the photographs, so that they can judge the reliability of the data set submitted from the RC in support of the drug approval application.

**ARE THERE ANY OTHER LEGAL REQUIREMENTS?**

When images are used to conduct screening programs for referable eye disease or to deliver ophthalmic care remotely, poor or inadequate images may result in improper patient care. For a person with diabetes, it is a good thing to be cleared as having no retinopathy by a reliable image-based screening program. However, it could be detrimental to be reassured that you have no retinopathy when you really do, but it has not been imaged well enough to detect!

**WHAT DO READING CENTERS TYPICALLY REQUIRE OF CLINICS FOR DIGITAL IMAGING?**

RCs have requirements regarding digital camera systems, photographic procedure and image transmission.

**Equipment**

The imaging sensors of a digital camera system must be capable of enough spatial and tonal resolution to capture the ocular pathology being studied. Spatial resolution is defined as the density of the picture elements (pixels) in the image. Conventionally, this parameter is expressed by indicating the number of megapixels captured by the camera sensor. Currently, for color digital images, RCs may accept a minimum of three to four megapixels, but would prefer to see the bar at five to six megapixels. The difference between these two levels is that the lower level makes it likely that the RC will see most of what it needs to see, and the upper level almost guarantees that it will see everything under normal conditions.

RCs may accept the lower spatial resolution level in some studies because they have no choice. For example, the clinic in question would be a good contributor to the study, but is limited to older equipment that cannot readily be replaced. However, for color imaging, RCs cannot accept systems below the 3-4 megapixel level. For this reason, legacy color systems providing one megapixel or less cannot be accepted because they do not have sufficient resolving power on the retina to allow discrimination of more subtle disease abnormalities such as retinal microaneurysms. Certainly, RCs recommend that if a clinic is buying new equipment it should aim for the higher level of resolution of five to six megapixels. In the future, RCs may express their spatial resolution requirements more uniformly, in terms of the number of microns on the retina represented by each pixel in the sensor, rather than in the raw megapixel capacity of the sensor. If the RC knows that your digital camera captures ten microns per pixel, it knows that your system has a resolving power of 20 microns on the retina, which is fine enough to capture even small microaneurysms. However, if the Reading Center knows only that the manufacturer rates the sensor at three megapixels, it may be unclear whether the image covers part of the sensor, all of it, or even extends beyond its edges, with each one of those variants yielding significantly different resolving power on the retina.

It goes without saying that the camera system needs to be in good working order, with all the parts working correctly, e.g., no “shutter bounce” or internal reflections. Optics should be free of dirt, via routine cleaning of the objective lens and maintenance of the other lenses as necessary. Relay lenses should be well adjusted to assure that the fundus image is centered in the field. If filters or lasers are used to obtain the image, they must be serviced regularly and filters changed on a regular basis.

**Procedure**

The photographer must be able to produce an image set that meets several criteria. The images need to have the following:

1. **Good technical quality:** (a) proper location, called “field definition,” so that the desired region of retina is captured; (b) sharp focus at the proper level of the retina, as much as practical given any media opacities present; and (c) marked stereo effect (if required).

2. **Good tonal resolution:** (a) moderately bright to bright illumination but without over-saturation or “blowout” artifact in the highlight areas; (b) deep contrast, so that retinal structures and disease abnormalities stand out against the retinal pigment epithelial background; and (c) proper color balance, so that retinal detail emerges clearly and the overall appearance is realistic.

3. **Adherence to the required study procedure:** (a) images should be taken at the required magnification or angle of view in order to capture the desired area of retina; (b) include the proper fields of view for the disease of interest such as the classic seven standard field protocol for diabetic retinopathy; and (c) be taken with stereoscopic effect as required, such as a stereo pair of the macula for evaluating retinal edema and serous detachment in age-related macular degeneration; and (d) adherence to the required sequence and timing of angiographic images to assure a consistent set of data throughout the entire study.

**Image Communication**

Historically, clinics sent analogue images to central RCs through the mail or by courier service, typically as slides mounted in plastic sheets. Of course, digital images can now be sent as data files, with the original file retained...
by the clinic and the copy sent to the RC. The Centers usually have several requirements relating to image transmission: (1) any patient identifying information must be removed and the patient anonymized according to study rules to protect patient confidentiality; (2) images must be saved and copied without being compressed, or if compression is allowed by the RC, using only the compression algorithm (e.g., PNG for lossless compression, or JPEG/JPEG2000 for “lossy” compression) and the level of compression that yields the quality level specified by the RC.

The mode of transmission to the RC may be via removable medium such as Universal Serial Bus (USB) memory stick or compact disc (CD), or electronic transfer over the internet, as required by the RC for the particular study. Either of these methods has its advantages and disadvantages. Sending CD’s may be more convenient for clinics lacking fast internet connections, but significant courier charges accrue. At the RC, once files are loaded on a server, the CD’s can be retained for back-up. Auditors can easily check the provenance (chain of custody) of images sent on CD, because a physical entity prepared and labeled by the clinic can be produced. Transmission of files over the internet, however, is definitely preferable in the long term. RCs have either already constructed the infrastructure to handle this, or are working towards this. The transfer mechanism must be very robust: secure against corrupted data or malicious attack, auditable as to the chain of custody, capable of rapid receipt of large files from multiple clinics simultaneously, and available 24 hours every day.

Looking towards the future, RCs recommend that clinics plan to obtain internet connections with the fastest upload speeds that are feasible for them, as more studies switch to digital transmission of more image types with larger file sizes.

**What are the Potential Problems?**

The transfer of digital images from clinic to RC usually goes smoothly. But, sometimes, problems arise that may require some troubleshooting from the RC. Images that are not properly masked and identified according to the given study protocol, of course, may not be accepted at the RC and will have to be de-identified and re-sent. RCs are also on the alert for the following: (1) any unauthorized compression, which can seriously compromise image quality; (2) any clinic enhancement of the image after it has been taken, using the tools in the digital imaging system or an external program such as Adobe Photoshop; (3) any change in spatial calibration that would affect accurate measurement of linear distances and areas.

RCs routinely check for these in several ways. Image compression can be detected via unexpected file name extensions (e.g., .JPG rather than .TIF), abnormally small file size (too few megabytes), and obviously degraded appearance of the image itself. Image manipulation such as contrast enhancement usually produces an abnormal appearance in the curves of the luminance histogram. Original images yield smooth curves, whereas enhanced or “stretched” images result in spiked curves. Altered spatial calibration is more difficult to catch – the RC may measure the distance between fixed retinal features (e.g., from the center of the optic disc to the center of the macula should measure approximately 4.5mm or 2.5 standard disc diameters) in order to see if the follow-up image set matches the baseline image set, and if all sets fall within the anatomically plausible range.

RCs must be vigilant because they are responsible for ensuring that the required images taken for a clinical trial have sufficient image quality to pass scientific muster.

Although RCs must be aware of such problems, and will notify clinics if they detect them, mistakes on the part of the clinics are typically inadvertent. Clinics want to do a good job, and if they do something contrary to RC policy, there is usually some reasonable explanation. In the case of image enhancement, photographers may even be doing what their ophthalmologists ordinarily expect or require them to do, forgetting that this particular image is being sent to a RC. System calibration may be thrown off when a company technician modifies the camera while servicing it (e.g., by switching relay lenses or changing settings), without asking or informing the clinic. Certainly, RCs do not assume suspicious intent, they simply want to work with the clinic to identify and correct the problem.

**What if the Reading Center is Asking for Images that are Very Different From What Your Ophthalmologist Prefers?**

Sometimes the local preferences of the ophthalmologist or clinical practice require that photographs or angiograms be performed in a routine way that is different from the protocol mandated by a clinical trial. In this situation, make every reasonable effort to shoot a “superset” of images that includes all the fields and timings required by either the clinical or the research study protocol. While this stratagem may result in a larger than usual set of images, it can be submitted in full to the RC, and edited for local use if desired. If the difference regards basic camera settings, such as color balance, you may need to follow a “dual mode” approach, in which you shoot it your way for your ophthalmologist and the RC way for studies. (This will be facilitated if your digital camera system has the capability of saving different settings and recalling them as needed.)

**What Should You Do if You Learn You Need to Be Certified by a Reading Center for Work in a Clinical Trial?**

Start the process as early as possible so you will not be put in a tight corner when the clinic is ready to recruit patients but you have not yet been successfully certified.
Alert your clinic’s principal investigators and study coordinators that you need to know about upcoming requirements as soon as practical. First, you’ll need to review the RC’s certification procedure and the imaging protocol for the specific study that you seek certification. Never assume it is the “same old” procedure. Occasionally, long-standing procedures are modified to improve their suitability. You or your study coordinator can obtain this material from the sponsor’s monitor assigned to your clinic, or if you know which RC will be handling the study in question, directly from the Center. The imaging protocol will provide instructions on the field definition, timing, identification and transmission of images, as well as the steps necessary for certification. If you have any questions, do not hesitate to call the RC prior to preparing your image submission. This communication may save time and effort later in the certification process.

**How Can You Make the Process as Successful as Possible?**

The next step is to practice shooting the protocol on clinic patients. However, specific, written consent from the patient and clinician may be necessary to preclude your clinics’ duty of care protocols. Ask your ophthalmologist to support you by providing clinic patients to practice shooting according to the study protocol. Many doctors are very supportive of your efforts to become comfortable with the shooting protocol if you tell them you are practicing to get certified. Post reminder notes in the examination room for your ophthalmologists to send you patients with appropriate pathology in order to practice shooting the protocol. If the photography requires stereo, and you do not routinely do stereo, practice stereo imaging with routine clinic patients. Give yourself enough time to perform the protocol on as many patients as you can, then select your best work to submit for certification. Make one final check to ensure that the images you submit conform to the imaging protocol.

Sometimes photographers struggle with patient conditions that make their work harder than it needs to be, such as sub-optimal dilation due to inadequate drops or too little or too much time after they are instilled, disturbed corneas from prior procedures such as tonometry, or patients worn out by other clinical demands prior to photography. Seek cooperation from your ophthalmologist and study coordinator so that you have enough time scheduled for the session to do study photography properly, and so that patients are well dilated, with clear corneas, and able to cooperate with the procedure.

Again, the keys to success with a clinical trial imaging protocol are knowing what is expected for a given study and being familiar with the imaging techniques required so that you are fully prepared and can anticipate each step during the procedure. Carefully study the RC’s certification protocol and the study’s imaging protocol – print them out and keep them handy for future reference. Remember that RCs want you to succeed, and are eager to answer your questions about their certification or imaging protocols.

**How Can You Learn to Do Clinical Trial Photography if You are Not Familiar With It?**

After reading the imaging protocol, it is often very helpful to seek advice from more experienced photographers. Some ophthalmologists have done photography, or know experienced photographers from their places of residency or fellowship. Most RCs have experienced ophthalmic photographers on the staff. Be sure to visit the specific RC web site for study-specific and general information on ophthalmic imaging. Examples from the authors of this article are: eyephoto.wisc.ophth.edu (University of Wisconsin, Madison) and www.darconline.com (Digital Angiography Reading Center). Other RCs also have websites. You can find their URL’s either in the printed material they have sent you or by entering their name as a browser search term.

The Ophthalmic Photographers’ Society (OPS) offers educational courses. There are also online copies of back issues of the Journal of Ophthalmic Photography available at the OPS website. The Joint Commission on Allied Health Personell in Ophthalmology (JCAHPO) offers course work in ophthalmic photography, including online modules. JMC Eye Photo, Inc. is a privately operated ophthalmic imaging education program listed on-line. Many academic institutions hold regular fluorescein conferences for continuing education. The textbook “Ophthalmic Photography” by Saine and Tyler is an excellent reference, as are the outstanding early articles on fundus photography and fluorescein angiography by Don Wong and Johnny Justice that are available in the ophthalmology sections of medical libraries.

**Conclusion**

RCs want to make the study imaging requirements as tolerable as possible. However, it is important to remember that RCs are accountable for the quality of the evaluation data they produce from examining your images. This responsibility is the primary rationale behind their requirements for your ophthalmic images. Different RCs may have slightly different requirements, but will have reasonably similar opinions on technical issues. Ultimately, they all have the same responsibility: collection of reliable research data from suitable ophthalmic images. Increasingly, RCs communicate with each other in an attempt to keep their protocols and requirements coordinated and in line with industry standards.

**References**