

EDITORIALS

The Clinical Site-Reading Center Partnership in Clinical Trials

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FORMER U.S. PRESIDENT MARTIN VAN BUREN ONCE wrote, "It is easier to do a job right than to explain why you didn't." This dictum is applicable to all aspects of clinical trials. The clinical site-reading center partnership focuses on collection of high-quality, standardized, unbiased imaging data. High-quality data collection by clinical sites according to standardized methodology has been central to the majority of studies leading to the most exciting advancements in ophthalmic patient care. The current model of multicenter clinical trials employing coordinating centers and reading centers has evolved partly to promote a high-level of data quality through training, certification, and monitoring of clinical site data collection. This Editorial will briefly review the roles of reading centers in clinical trials, the purpose of imaging protocols, certification, and image quality monitoring, quality control within reading centers, clinical site responsibilities, and the impact of new technology in large clinical trials.

As residents in residents in ophthalmology during the 1980s at the University of Wisconsin, we were steeped in the importance of standardized independent evaluation to minimize bias and variability in clinical trial assessments. The seminal reports from the Diabetic Retinopathy Study, Early Treatment Diabetic Retinopathy Study, Wisconsin Epidemiologic Study of Diabetic Retinopathy, Diabetic Retinopathy Vitrectomy Study, and Macular Photocoagulation Study had radically changed the standard of care for diabetic retinopathy and neovascular macular degeneration, and they relied heavily upon photographic assessments from reading centers. Later, however, in the role of clinical investigator recruiting patients for clinical trials from a busy retina subspecialty practice, I was shocked to learn the minute details specified and required by reading centers – photographic field definition, stereoscopy, film type (sometimes by film lot number), processing by certified labs, labeling and sorting of slides, etc. Meeting these requirements was sometimes a frustrating burden upon the clinic staff and patients and sometimes seemed downright obsessive. My liberation came with the gradual appreciation of the relationship between process and procedure at

the site and data quality. These minute requirements existed because the experience of the reading center taught that systems can fail without them. This renewed my appreciation for the clinical research coordinator and photographers who maintained the high-level of data quality from our site despite my occasional impatience. Our staff understood Van Buren's quip better than I did. My role has changed again and now, as Director of the University of Wisconsin-Madison Fundus Photograph Reading Center, I have the opportunity to respect and admire the many clinical investigators and their staff that are able to meet the requirements of clinical research with enthusiasm. Such sites share in common the attributes of adequate staff time dedicated to clinical research, thorough familiarity with the study protocol and procedures, and experience.

Ophthalmic reading centers are diverse and include centers for interpretation of optic nerve head topography, visual fields, corneal endothelial images, and a variety of retinal images. Reading centers provide image evaluations that are uniform across clinical sites by evaluators who are easily masked to treatment assignment and other clinical information. They have the potential to employ more detailed observations than what might be possible in clinics and to develop disease classifications from them; a prime example has been the Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy severity scale from stereoscopic color photographs,¹ which has been used as a major outcome in multiple important trials of diabetes complications.

The requirements for image analysis in clinical trials are specific to each study. The importance of morphology outcomes for a study weighs in the balance. If the primary outcome is a functional assessment such as vision, there may be no need for a reading center to evaluate images. In studies where morphology is the primary outcome, the need for masked standardized independent assessment should be carefully considered. Imaging data may be useful for the development of disease classifications, hypothesis generation, and subgroup analyses. Masked independent evaluation to control bias is particularly important when the treatment benefit is small, a function which often can be more easily and reliably performed in a reading center environment.

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The problem of variability in clinical assessments can be partially overcome through the use of trained observers using a strict protocol in a centralized setting to promote uniformity.^{2,3} Historically, reading centers have excelled in the interpretation of clinical images in a manner somewhat analogous to the physician observer but with greater detail and complexity than is possible in the clinic. The reading center evaluation may be repeated and the reproducibility measured; an extremely difficult process to replicate in the clinic setting. Knowing the reproducibility of measurements is important when statistically analyzing imaging data and in judging significance of the data from a clinical perspective.^{2,3} Reading centers continually test and report the reproducibility of grading for each data item. A systematic quality control program is necessary as part of the grading process.

The reading center prepares protocols for image capture and submission, trains the site staff on these procedures, and certifies the imagers. The imaging protocol is detailed and written clearly so as to standardize data collection as much as possible. Digital imaging requires the protocol to be specific to the make and model of the equipment because most camera and optical coherence tomography (OCT) manufacturers in ophthalmology have developed proprietary software that produce unique non-standardized file formats. Certification is the formal process by which the clinical site staff demonstrate understanding and ability to adhere to the study protocol before the first patient is enrolled. The certification process may be quite simple for some imaging methods, and very difficult for others. Inexperienced imagers may make multiple attempts and even then fail to become certified – a source of frustration for all involved. Because of the pressures on modern clinical practices for increased efficiency and productivity in the face of declining revenue, the clinical site staff member pressed into the role of imager is sometimes incompletely trained for clinical trial work. Clinical practice demands for imaging, which emphasize capture of the abnormalities of particular interest in an individual patient, are often different from the rigorous standard protocols typically used in clinical research. The diligence required by the imager to become certified for clinical trial protocols, with feedback and advice from the reading center, often improves the quality of the work performed for patient care purposes. Reading centers also monitor and report upon image quality throughout the course of a trial in order to identify and help correct problems quickly should they occur.

Image quality issues are a common source of variability and missing data in clinical trials. For instance, if images of an eye at one visit show retinal neovascularization, but at the next visit the image is poorly focused or the photographic field does not capture the area in question, there may be a spurious “disappearance” of the neovascularization that mimics the therapeutic effect of an intervention. If the images are severely flawed (fortunately, a rare event), the reading center may not be able to produce data for those visits. Missing data can have a deleterious impact upon the statistical analyses

and results in a clinical trial, and, if there is enough missing data, the outcomes of the trial may be called into question.⁴ An error in obtaining baseline images may severely limit the usefulness of imaging data on that patient. Of particular interest from an image quality standpoint is the transition from color film fundus photography to digital color fundus images in clinical trials. Because digital camera chips handle illumination, contrast, and color balance quite differently from film,⁵ obtaining images similar to film quality with digital cameras has been challenging. Post hoc image enhancement at the reading center can improve the illumination, color balance, and contrast of substandard digital images.⁵ This may help preserve continuity of grading with historical film data sets and minimize variability within studies using both film and digital photography. The best solution is for the imagers at the clinical sites to educate themselves regarding the assessment and modification of tonal balance and how this is accomplished with the equipment available at the clinic to produce the highest quality photographs – this is beneficial for both research and clinical care purposes.

Technological advances have led to instruments that make automated measurements that formerly were clinical assessments. For example, macular edema assessment by OCT is clearly a better method for measurement of retinal thickness at the center of the macula than stereoscopic color photographs or the eye of the clinician. In general, the human mind/eye remains (for the moment) superior to software for purposes of lesion classification in complex images under a variety of quality conditions, for solving quality issues, and for handling unusual disease presentations. Looking forward, it is inevitable that automated lesion detection, classification, and measurement will become increasingly reliable and used more frequently in the clinic setting. Is there a future role for reading centers in the context of increasing technologic innovation and automated measurement? Actually, new imaging technology (eg, OCT, fundus autofluorescence) seems to increase, rather than decrease, the demand for reading center services. This is in part attributable to the uncertainty of how best to classify disease with the new methodology, and to identify and rectify new imaging quality issues that present with new technology. Even if the only morphologic outcome variable to be analyzed is an automated measurement obtained directly from an instrument at the clinical site, a reading center may be of value for certification and quality control of imaging.

The evidence base upon which medical care of patients is founded is increasingly dependent upon the data from carefully designed and conducted multicenter clinical trials.⁶ Ocular imaging analysis in support of such trials must be of demonstrable high quality. Without this assurance, a study runs the risk of running afoul of Van Buren’s credo. In the end, it is the diligent efforts of clinical site investigators and staff, and the patients that donate time and their own resources, that create the foundation of ophthalmology clinical research.

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