

The role of central reading centers – current practices and future directions

Colin S Tan^{1,2}, Srinivas R Sadda³

Central reading centers (CRCs) have several crucial roles in the conduct of clinical trials, providing key input during the study design, preparation of the operations manual, as well as site and photographer certification. They provide objective, standardized grading of images from study subjects, which determines study eligibility, and also evaluate lesion features at subsequent study visits. CRCs need to adhere strictly to Good Clinical Practice (GCP) guidelines, as well as the established standard operating procedures in order to ensure that images are graded properly. The role of CRCs will continue to evolve, and include the use of web-based image transmission and grading platforms.

Key words: Central reading center, randomized controlled trial, standard operating procedure

Access this article online

Website:

www.ijo.in

DOI:

10.4103/0301-4738.159866

Quick Response Code:

Clinical trials in ophthalmology frequently use central reading centers (CRCs) to grade study investigations, particularly imaging data. The image sets are reviewed at the initial screening visit to determine study eligibility, as well as at subsequent time points in the study, to evaluate response to therapy.

Earlier studies such as the macular photocoagulation study^[1] used film-based imaging protocols, which required transmission of hard copy images via conventional mail, often resulting in delays in the grading process.^[2] With the advent of digital imaging systems, it became possible to transmit electronic images of these investigations more rapidly, which improved the turnaround time for study reports to be completed. The range of imaging modalities has increased – in addition to color fundus photographs and fluorescein angiography, many studies now employ optical coherence tomography (OCT),^[3,4] fundus autofluorescence,^[5,6] and indocyanine green angiography (ICGA).^[7]

Rationale for central reading center in clinical trials

A CRC is now essential for the conduct of multicenter clinical trials and can make major contributions to the success of that study. An obvious benefit is to provide standardized, anonymized and objective grading of study images by trained graders who are neither aware of nor influenced by knowledge of the patient characteristics or treatment arm assignment. This produces more accurate and unbiased grading. In addition, since all images in the study are graded by a small group of graders using standardized grading protocols, there is less variability in the interpretation of the imaging modalities.

Central reading centers also play crucial roles in the administrative planning and setup of the study. In particular, the operations manual should contain detailed imaging procedures and protocols to ensure that all study sites employ the same methods of acquiring the study investigations. This includes, but is not limited to, the list of approved equipment for each investigative modality, the instrument settings and parameters, how the images are labeled, and transmittal procedures.

Standardization of, or at least restricting the choice of, approved equipment is crucial to ensure comparability of the imaging modalities. For example, it is well-known that retinal thickness measurements vary with the choice of OCT device, particularly when comparing older time domain OCT with current spectral domain OCT^[8,9] or swept source OCT.^[4] This is because of differences in the segmentation algorithms used in each OCT device, and variations in where the segmentation boundaries are drawn. The use of different types of OCT devices in a study would result in difficulty in comparing retinal thicknesses among patients from different sites.^[8]

Another example of the benefits of standardization is seen in the EVEREST study, the first multicenter randomized controlled trial for polypoidal choroidal vasculopathy.^[7] In this study, all sites utilized the Heidelberg retinal angiograph (Heidelberg Engineering, Heidelberg, Germany) instrument, as the dynamic ICGA performed at the beginning of the angiogram was crucial for visualization of two of the study diagnostic criteria – the presence of a branching vascular network and pulsation of the polyps.^[7,10] This illustrated the crucial role that CRCs play in providing scientific input on the study design and objectives to the study sponsor, so as to ensure that the parameters desired can be graded based on the imaging protocols and criteria.

Requirements for central reading centers

A CRC requires a set of standard operating procedures (SOPs), which covers the administrative, imaging, grading, quality, and data management practices of that center. These form the backbone of the CRC for daily workflow, although they can be modified as required for study-specific operations manuals, based on discussions with the study sponsor.

¹National Healthcare Group Eye Institute, Tan Tock Seng Hospital, ²Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore, ³Doheny Eye Institute, University of California Los Angeles, Los Angeles, California, USA

Correspondence to: Dr. Colin S. Tan, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433. E-mail: colintan_eye@yahoo.com.sg

Manuscript received: 30.01.15; **Revision accepted:** 21.05.15

While the SOPs vary between reading centers, a key facet is an adherence to Good Clinical Practice (GCP) guidelines, as well as relevant regulations in the country of practice. These are essential steps that will be audited by study sponsors as well as health authorities, such as the United States Food and Drug Administration, pending approval of the study drug.

The training of graders is of paramount importance to ensure that the grading is consistent and accurate. A proper program of training and certification of graders must be established prior to the CRC embarking on any clinical study. While the specific components of grader training and certification may vary between reading centers, common features include information on the reading center SOPs and protocols, background knowledge of the clinical conditions being graded, and detailed grading procedures for each imaging modality. Graders in training are expected to review these protocols, and take a series of tests which assess their knowledge and understanding of these. They will subsequently proceed to grade training sets, which the senior grader will review with the trainee. Once they have met the minimum requirements, they can then proceed to an assessment for each modality. Upon passing these, they are then certified for that respective modality.

Challenges faced by central reading centers

Central reading centers routinely face administrative challenges posed by nonadherence to the study protocols, which pose potential threats to the integrity of the analyses. A common example is incorrect labeling of study images. While some minor errors can be managed internally at the CRC, it is essential to have the proper serial numbers of the subject, without which it is not possible to confirm that this is indeed the correct subject. In such an event, grading cannot proceed. Another example is the inclusion of patient identifiers, which would violate both national as well as clinical trial regulations.

Another challenge occasionally faced by the CRC is a disagreement from the recruiting clinical site investigator regarding the eligibility determination made by the CRC. It is essential to reassure site investigators that the role of the CRC is not to evaluate their clinical acumen or professional judgment, but rather to ensure that the patient meets the required study criteria, as determined by that particular clinical trial.

Future trends

Multicenter randomized clinical trials are the gold standard when evaluating treatment modalities, and there will be continued need for Level I evidence to support new therapies in the future. Just as earlier, CRCs had to adapt to digital imaging and new imaging modalities,^[2] current CRCs will also need to peer into the crystal ball to see future trends and plan to evolve. A trend that is already taking shape today is the use of web-based/cloud-based file sharing systems, which allow virtually instantaneous transmission of data to any part of the world. Some CRCs already employ web-based digital transfer and grading systems, and these will likely evolve in the next few years. Cloud-based systems will also allow sharing of images and data for collaborations between different CRCs.

Another future trend will be automated or semi-automated grading of study images by software specifically designed for this purpose. These have potential benefits as well as pitfalls. In particular, automated grading has the potential to reduce cost and speed up the grading of images, possibly more objectively,

and free upgraders to perform only adjudication of questionable features. The risks, however, include the accuracy of grading, particularly when the lesion falls outside of the usual parameters set for the program. The acceptance of the accuracy of the grading output, by study sponsors, by the medical community, and by the public, is also an area of concern.

Conclusion

Central reading centers play a crucial role in the conduct of clinical trials, ensuring standardized, objective grading of study parameters. Their roles continue to evolve with new technology and imaging modalities.

Acknowledgments

Dr. Colin Tan is the Head of the Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore. Supported in part by the National Healthcare Group Clinician Scientist Career Scheme Grant CSCS/12005 (Dr. Tan). Dr. Tan receives travel support from Bayer, Heidelberg Engineering and Novartis.

Dr. Sadda is the Director of the Doheny Imaging Reading Center, Doheny Eye Institute, USA. Dr. Sadda has served as a consultant to Allergan, Genentech, Optos, Carl Zeiss Meditec, and Alcon.

References

1. Recurrent choroidal neovascularization after argon laser photocoagulation for neovascular maculopathy. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1986;104:503-12.
2. Slakter JS, Carvalho C, Coleman H. The Digital Angiography Reading Center (DARC) role in the anecortave acetate clinical trials. *Surv Ophthalmol* 2007;52 Suppl 1:591-8.
3. Tan CS, Cheong KX, Lim LW, Li KZ. Topographic variation of choroidal and retinal thicknesses at the macula in healthy adults. *Br J Ophthalmol* 2014;98:339-44.
4. Tan CS, Ngo WK, Cheong KX. Comparison of choroidal thicknesses using swept source and spectral domain optical coherence tomography in diseased and normal eyes. *Br J Ophthalmol* 2015;99:354-8.
5. Tan CS, Heussen F, Sadda SR. Peripheral autofluorescence and clinical findings in neovascular and non-neovascular age-related macular degeneration. *Ophthalmology* 2013;120:1271-7.
6. Heussen FM, Tan CS, Sadda SR. Prevalence of peripheral abnormalities on ultra-widefield greenlight (532 nm) autofluorescence imaging at a tertiary care center. *Invest Ophthalmol Vis Sci* 2012;53:6526-31.
7. Tan CS, Ngo WK, Chen JP, Tan NW, Lim TH; EVEREST Study Group. EVEREST study report 2: Imaging and grading protocol, and baseline characteristics of a randomised controlled trial of polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2015;99:624-8.
8. Tan CS, Li KZ, Lim TH. A novel technique of adjusting segmentation boundary layers to achieve comparability of retinal thickness and volumes between spectral domain and time domain optical coherence tomography. *Invest Ophthalmol Vis Sci* 2012;53:5515-9.
9. Tan CS, Li KZ, Lim TH. Calculating the predicted retinal thickness from spectral domain and time domain optical coherence tomography – Comparison of different methods. *Graefes Arch Clin Exp Ophthalmol* 2014;252:1491-9.
10. Tan CS, Ngo WK, Lim LW, Lim TH. A novel classification of the vascular patterns of polypoidal choroidal vasculopathy and its relation to clinical outcomes. *Br J Ophthalmol* 2014;98:1528-33.

Cite this article as: Tan CS, Sadda SR. The role of central reading centers - current practices and future directions. *Indian J Ophthalmol* 2015;63:404-5.

Source of Support: Nil, **Conflict of Interest:** None declared.