Video Blog - Subject Eligibility Review and Diagnostic Adjudication

What is Subject Eligibility Review and Diagnostic Adjudication?

Subject Eligibility Review and Diagnostic Adjudication is a very long name for one of the services we offer at Cogstate as part of our rater training and central monitoring programs. In brief, what this service does, is add an independent check of some of the key screening data by our expert clinicians to make sure that a subject the site believes is a good candidate for the study actually fits with the key clinical eligibility criteria of the protocol.

How does that work in a clinical trial?

The best way to explain the service is provide an example from an actual study. Cogstate recently worked on a large global clinical trial of a potential disease-modifying agent in a sample of subjects with early Alzheimer's disease. In this particular study, the subjects were stratified prior to randomization on the basis of their initial disease stage; either Mild Cognitive Impairment due to Alzheimer's disease or Mild Alzheimer's disease.

After the initial screening visit, sites were required to submit to Cogstate all of the relevant clinical assessment data for any subject the site believed was a good candidate to move forward in screening after that initial visit. The data submitted to Cogstate included copies of source documentation along with digital audio recordings of the assessments for the Mini-Mental State Examination, Clinical Dementia Rating, and a test of verbal new learning and memory. Each of these assessments had specified ranges or cutoff scores for eligibility defined in the protocol. The site physician who was responsible for assigning the subject's research diagnosis of either MCI or Mild AD had to complete and submit for our review a Diagnostic Rationale Form. This is a form we designed here at Cogstate to document key aspects of the subject's clinical history and current presentation, like approximate date of onset of symptoms, the nature of progression over time, domains of current cognitive or behavioral impairment, impact of those impairments on daily life functioning, and any concurrent medical or neurologic disease or factors that could potentially have an effect on cognition and functioning.

Once the submission was complete, a regionally-based neuropsychologist, who is a member of Cogstate's Local Expert Advisor network, reviewed the submitted files to make sure the assessments had been administered and scored correctly, and compared the final scores to the study eligibility criteria to make sure the subject indeed met those criteria. The neuropsychologist also reviewed the assessment results together with the information documented on the Diagnostic Rationale Form to independently determine whether the subject better fit a research diagnosis of MCI due to AD or Mild AD, according to the National Institute of Aging & Alzheimer's Association criteria published in 2011.

If the subject was deemed "questionable" in any way by the reviewing neuropsychologist, then the case was raised for adjudication. That meant that a second neuropsychologist, one of the science directors at Cogstate working on the study, would examine the data and then confer with the original reviewer. To determine that a subject did not meet eligibility criteria and should ultimately be screen failed, or that an alternative research diagnosis should be applied for the subject, a consensus opinion had to be reached between those two experts. The site was then notified of the adjudication outcome and provided with a thorough rationale for the decision.

What were the results of the Subject Eligibility Review and Diagnostic Adjudication service for that study?
The screening data for nearly 3500 potentially eligible subjects were reviewed by Cogstate's experts for this particular trial. About 11% of those were identified as questionable in some way by the initial reviewer and were raised for adjudication. In about 40% of those questionable cases, the issue was a screening assessment score that was incompatible with the protocol eligibility requirements, and for the other 60%, the research diagnosis was deemed to be potentially incorrect. When it was a test score that did not meet eligibility criteria, it was most often that the memory test score did not meet the criterion of being 1 or more standard deviations below the age-

appropriate mean score. About 20% of the time, though, it was the MMSE score that was not in the protocol-required range, either because the site did not realize it or the items had been scored incorrectly. In another 15% of the cases, the obtained CDR domain and global scores did not meet the requirements of the protocol. In those cases where the initial diagnosis assigned by the site physician was found to be questionable, the adjudication process confirmed that the diagnosis should be changed in about 2/3 of the cases. In the other third, after the case was discussed between the two experts, the site's original diagnosis was retained.

How long does it take to perform Subject Eligibility Review and Diagnostic Adjudication?

From the time a complete set of screening data is provided to Cogstate for review, the entire process is typically completed within 4-5 business days. The initial review by the local neuropsychologist is completed within two business days. So, if the subject is found to be eligible and the site-assigned research diagnosis is determined to be correct, then the site can be notified right away. If the subject needs to be adjudicated, that often requires a teleconference between the independent reviewers or an exchange of information by email. Given the global nature of the study and the time zone differences between the two reviewers in some cases, the adjudication process can take up to another 2-3 business days over and above the time it takes to do the initial review.

What are the benefits of Subject Eligibility Review and Diagnostic Adjudication to the study sponsor?

One of the reasons clinical trials fail, and there can be many different ones, is that inappropriate subjects get into the study. The key benefit to the sponsor is that it protects the integrity of the study by identifying subjects who violate the protocol in some way, and preventing them from being inappropriately randomized to treatment. Another important benefit, at least in studies of disease-modifying drugs for Alzheimer's disease, where screening occurs in multiple stages, is cost savings. By identifying inappropriate subjects early, typically within a few days of the initial screening visit, it prevents more costly procedures like MRIs and PET scans from being performed unnecessarily later in the screening period. Similarly, it benefits the subjects who will never be eligible for randomization from having to go through additional procedures that can be invasive or otherwise unpleasant.