

PODCAST TRANSCRIPT: MEASURING COGNITION IN ONCOLOGY TRIALS

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Benjamin Hunting: Welcome to the Cogstate podcast series on “Measuring Cognition in Clinical Trials”. I’m Benjamin Hunting and today’s podcast is the third in our series where we’ll cover “*Cognitive Measures in Oncology Trials*”. Our speaker today is Dr. Brian Harel. Dr. Harel is the Clinical Science Director at Cogstate and Assistant Clinical Professor at the Yale University School of Medicine, Child Study Center. As a clinical neuropsychologist, Dr. Harel’s current areas of research interest include oncology and pediatrics, and through his work at Cogstate he collaborates with numerous key governmental and leading academic institutions and consortia, including the National Cancer Institute, Children’s Oncology Group, Mayo Clinic, Harvard Medical School, the Proton Collaborative Group and numerous other institutions worldwide.

Brian, thanks for joining us today. And to start things off, I was hoping we could discuss which types of oncology trials most often add value by measuring cognition?

Brian Harel: Thank you Benjamin. So cognitive testing is most commonly included in trials where the cancer effects the central nervous system, so things such as primary brain tumors or cancers that metastasizes to the brain. There’s also value though in including cognitive testing where there’s concern about possible adverse effects of the treatment on the central nervous system. Or where the new treatment is thought to have a better side effect profile than the current standard of care. So for example, in cases where the old treatment may cross the blood brain barrier, but the new one is thought not to cross the blood brain barrier and therefore has a better side effect profile. Cognitive impairment is associated with a disease where the cancer is in the brain, so for instance, 60-100% of primary brain tumor patient’s evidence cognitive impairment. In addition, upwards of 90% of patients with brain metastases evidence cognitive impairment. There’s also concern about cognitive impairment, as I said, when the drug potentially crosses the blood brain barrier and in those cases you can see adverse side effects such as sedation or fogginess associated with the drug. The profile of cognitive impairment consists of non-focal cognitive deficits such as they lose effective processing speed, attention, learning and memory, working memory, and executive function, as well as an overlay of focal cognitive deficits which are influenced by things such as the tumor location or possible side effects of the tumor such as seizures.

Benjamin: And why is it important to measure cognitive change in oncology clinical trials?

Brian: Now overall survival, progression-free survival, and radiographic response, which are the most common endpoints in oncology trials, may not fully capture the impact of therapy trials where there’s an effect on the central nervous system, either due to the disease or treatment. And in fact, improved survival doesn’t necessarily lead to improved patient functioning. For instance, you could imagine a treatment that would extend survival but at the cost of significant cognitive impairment and loss of functional independence. The FDA has recognized this and as such note that clinical benefit cannot be determined by imaging or survival alone. They do say however that improvement in neurocognitive function or delay in neurocognitive progression would be acceptable endpoints. And in fact, as we get better at keeping people alive, outcomes examining patient functioning and well-being are going to become increasingly important because by extending people’s lives we want to make sure that we aren’t doing it at the cost of their ability to interact with the world around them. Clinical benefit is also important in cases where there’s very short survival, as is the case with glioblastomas. Here the importance of capturing cognitive data becomes critically important a symptom management and maintain quality of life become critical to understanding treatment benefit.

Benjamin: So would it be safe to say that in measuring cognitive change in an oncology clinical trial, you’re kind of moving past viewing patients simply as subjects and more addressing the human aspects of the treatment in question?

Brian: Yeah that’s right. So what we’re saying by saying measuring cognition is important is we’re saying that it is not enough to simply keep them alive, but we want to keep them functioning well also.

Benjamin: And what are the most commonly utilized Cogstate tests for oncology trials and why?

Brian: So the Cogstate tests that are commonly used in these trials assess memory, working memory, executive function, processing speed, and attention. And the reason that these cognitive domains are assessed is because a number of groups, including The International Cognition Cancer Task Force, argued that these cognitive domains are important to assess. Now, in assessing those domains we use a number of different Cogstate tests. One battery of tests that we commonly use includes the International Shopping List test, the detection test, the identification test, and the one-back test. The International Shopping List test is a verbal list-learning test that assesses verbal memory and was chosen for this battery because of the considerable amount of work that was done in oncology trials using the paper and pencil battery developed by M.D. Anderson. Arguably the most sensitive test in that battery is the Hopkins Verbal Listening test, which is also a list learning test and in fact there is a paper published by Kane Et Al in 2015 in the Journal of Neuro-Oncology which shows that the International Shopping List test is highly correlated with the Hopkins Verbal Listening test, so that's one battery that's commonly used. Another battery that's been commonly used in a number of trials we're supporting is a very similar battery that included the identification, detection, and one-back test, which are measures of processing speed, attention, and working memory, respectively. But instead of using the International Shopping List test to measure memory, we use this one-card learning test to measure memory. The one-card learning test is a measure of visual memory. The benefit of using the one-card learning test over the International Shopping List test is that it does not require one-on-one assessment, so it could be administered in groups, it could potentially be administered at home, so it allows for a more flexible assessment environment. Both batteries have been quite popular. The reason Cogstate has been increasingly chosen as opposed to the paper and pencil test is because there are a number of advantages that using computerized testing convey. So it makes the administration more standardized, offers increased speed of assessment, allows ongoing monitoring of the study data as well as resolution of the data discrepancies in real time. And perhaps most importantly, it allows for the elimination of errors related to scoring tests and data entry.

Benjamin: And so, when we talk about demonstrating Net Clinical Benefit, what other measures are typically used in an oncology trial?

Brian: So when we're talking about the clinical benefit of a drug in an oncology trial, the FDA has said that it's important not just to look at cognition, but that also looking at health related quality of life is an important outcome in cancer research. And so when we're talking about clinical benefit we're really talking about objective cognitive testing, also looking at health related quality of life, and also looking at symptom burden. So you can think of the objective assessment of cognition as a metric for measuring the neurologic integrity and it's been shown that objective cognitive testing is associated with both academic and occupational success, so it has real world consequences. Helpfully the quality of life, which is typically measured using patient reported outcomes, really captures the impact of the disease and the treatment on the social, psychological, and physical aspects of a patient's life. Importantly because it's a patient reported outcome, it really reflects the patients' perception is how they're doing in those areas. Some of the symptom burden is assessed using patient reported outcomes typically, and it captures the physical and psychological symptoms associated with the diseases or the treatment. Really requires all three to get a complete picture of the clinical benefit of a treatment.

Benjamin: Could you tell us about any cancer research collaborations or consortia where Cogstate is currently involved?

Brian: Yes, so we're doing a number of different studies with a variety of academic institutions all over the world, including institutions such as St.Jude's and DC Children's. We're also had the opportunity to work with a large number of consortia such as The Children's Oncology Group and NRG. So, we have three ongoing studies with The Children's Oncology Group that we've had the fortune of participating in. One is looking at the effects of Medachino on neuro-cognition in children with primary brain tumors. We're also working on another trial looking at the longitudinal changes in neurocognitive function in children and adolescents with high risk ALL. And then we're beginning to initiate a study looking at the effects of arsenic on patients with APF. In adults we're working on two studies with NRG, specifically with their radiology therapy oncology group. One is looking at the natural history of post-operative cognitive function and quality of life in patients with Supratentorial Low-Risk Grade II Glioma. We also just completed a Phase II trial of

hippocampal avoidance during whole brain radio-therapy for brain metastases and the results of that; actually that study has been published in the paper referred to earlier for Kane Et Al 2015, published in the Journal of Neuro-Oncology. These collaborations are critical for validating our tools in their populations. They also give our collaborators the opportunity to assess cognition in situations that would otherwise not be possible, such as in large cooperative studies where there's neither the time nor the expertise across all of the participating instructions to use lengthy neuropsychological test batteries. The use of Cogstate in these types of studies is not only expected to improve data accrual but it will also allow for the characterization of cognitive function during treatment, for which there's very little data at this time.

Benjamin: Dr. Harel, just to wrap up this podcast: finally, what are some important considerations sponsors should consider when including cognitive assessment in oncology trials?

Brian: Well there are a number. I think one important one is the consideration of the test you select. So you want to select tests that have been successfully used in oncology clinical trials in the past and have been to regulators. To that end, I think there are a number of tests. The M.D. Anderson battery is probably the most commonly used battery in oncology trials. It's a paper and pencil battery that includes measures on memory, processing speed, attention, and executive function. The Cogstate tests that I have described earlier have also been used in a number of oncology clinical trials and so regulators have seen those tests as well. I think you also want to pick tests that are easy to administer. So I think it's important to remember that assessing the cognition in oncology trials that sites are often not going to be as familiar with the tests as sites that typically do studies for neurologic or psychiatric diseases. And so it's very important to use tests that are easy to administer, so that you can get rater trainer buy-in, but also that don't require a lot of work, and don't allow for a lot of errors. So to the extent that they are computerized and scoring and administration can be automated that is a considerable benefit. Depending on the disease, you may also have to do frequent re-evaluations, so for example in glioblastomas or diseases where the cancer metastasizes to the brain and median survival is quite brief, we need to provide frequent re-evaluations and in those cases you want tests that have good stability over brief periods of time. In other words, you want tests that don't have significant practice effects. You also want to consider what types of measures you want to include. So as we discussed earlier, the FDA has said it's important to assess not just objective cognitive skills but also quality of life, so including patient reported outcomes that assess health related quality of life in addition to objective cognitive measures is important. It's also important to appreciate that they don't measure the same things so you couldn't use patient reported outcomes in lieu of objective cognitive assessment. It's also important to think about whether you're looking for maintaining cognitive function in the face of a neurodegenerative condition or you're looking to improve treatment related cognitive decline. So are you looking at stability or improvement; and then also considering statistical significance vs. clinical significance? So overall, I think it's important to consider the regulatory, scientific, and operational issues around inclusion of cognitive assessment in these trials. Openly, I think this is an exciting time for oncology with the introduction of all of these new immunotherapies and I truly believe that the inclusion of cognitive assessment will become an integral part of cancer trials moving forward.

Benjamin: Dr. Harel, I thank you for taking the time to speak with us today and the audience appreciated your input and insight into cognition and oncology trials.