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The Case for Cognitive Assessments in Phase I Clinical Trials

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Patient-focused drug development is increasingly important to regulators. The drug development process now emphasizes patient-reported outcomes, which are an essential part of evidence that should be included as part of new drug applications [1, 2]. Early evidence of a compound's impact on patients' quality of life, including cognitive function, is vital for both patients and regulators.

Phase I clinical trials mark the first step toward regulatory approval for new drugs. Conducted in healthy volunteers, these trials primarily focus on evaluating safety, tolerability, and responses to varying dosages. The results from early-phase trials inform decisions about progressing an investigational compound to later phases.

Cognitive changes due to disease or treatment, regardless of the indication, are often overlooked in Phase I drug development. However, these changes can significantly affect patients' quality of life and the clinical drug development process. Early detection of drug-related cognitive adverse effects is crucial to avoid issues later [3, 4]. Cognitive safety studies provide essential information, helping patients and physicians evaluate a drug's benefit-risk profile for prescribing decisions.

Despite their importance, many drug development programs do not include sensitive measurements to assess cognitive function. The good news is that awareness of the importance of cognitive outcomes is growing among regulators, sponsors, and patients, especially in early-phase trials. In this blog, we will explore the significance of cognitive assessments in Phase I trials, examining their role in evaluating safety, identifying potential efficacy, and informing critical decision-making processes.

Why include cognitive assessments in Phase I clinical trials?

Cognitive deficits observed in Phase I trials are typically more discrete, often affecting only one or two specific domains, unlike those seen in dementias. However, understanding their impact is crucial for identifying potential effects on patient quality of life. Discovering cognitive deficits late in the clinical drug development process is costly and increases the risk of the drug not being approved, thereby slowing down the compound's progression.

Traditional scales like the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment lack the sensitivity to detect subtle or mild cognitive change [5]. Therefore, employing sensitive tools such as computerized cognitive test batteries can identify deficits early and provide reliable, unbiased data to clinicians and drug developers.

Phase I studies encompass a range of endpoints, including safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) modeling, abuse liability, and proof of concept. Integrating computerized cognitive testing into these studies, alongside other PD measures like EEG, fMRI, and actigraphy, provides sponsors with critical insights and opportunities including:

- Gaining a comprehensive understanding of a drug's effects on cognitive function and the implications for safety, tolerability, and efficacy across a broad dose range
- Establishing proof-of-principal and concept
- Identifying subtle cognitive impairments or poor cognitive side effects that can inform go/ no-go decision making
- Halting clinical trials and redirecting resources to more promising compounds
- Confirming the absence of unwanted cognitive side effects

Computerized cognitive assessments have been instrumental in generating data for product labeling and regulatory approval, highlighting their importance in the drug development process. In fact, many compounds on the market have utilized Phase I data, including safety, PK/PD, and drug-drug interaction trials, to support claims [6].

In Phase I, cognitive assessments are essential for identifying drug-induced cognitive changes. As drug development progresses, cognitive testing continues to play a crucial role in confirming safety, efficacy, and collateral benefits associated with the drug.

Selecting an effective computerized cognitive test solution

Effective computerized cognitive assessment solutions should provide specific capabilities to fulfill their objectives. They should:

- Be brief and simple to administer, yet highly sensitive
- Allow for testing at multiple time points to establish relationships with other PK and PD measures without inducing practice/ learning effects
- Demonstrate good test-retest reliability, as well as bi-directional sensitivity
- Be repeatable, allowing a profile of a compound to be built over time and across multiple dosing schemes
- Assess distinct cognitive domains across different patient populations
- Be available in multiple language versions
- Not be cost-prohibitive

Signant Health's CDR System®: A computerized cognitive assessment solution

The Signant SmartSignals® CDR System®, backed by 40 years of validation data, is a comprehensive and proven solution for cognitive assessment across all phases of clinical trials. Well-received by volunteers, patients, and clinicians, the CDR System can be seamlessly integrated into Phase I trials without requiring additional volunteers, extending trial duration, or needing specialized units or staff.

Its cognitive safety battery, widely used in Phase I trials, takes just seven minutes and assesses information processing speed, vigilance, and accuracy through three tasks: simple reaction time, digit vigilance, and choice reaction time. This provides sponsors with early-phase signals to guide safety, tolerability, and dose selection decisions. Its versatility and ease of implementation make it a valuable tool for assessing cognitive function throughout drug development, and its industry-leading normative database ensures accurate interpretation of study data

Summary

Computerized cognitive assessments are of paramount importance in Phase I clinical trials, offering valuable insights into the safety, efficacy, and potential cognitive effects of investigational drugs. As drug developers strive to bring new therapies to market, the judicious use of cognitive assessments early in the development process can provide critical information for decision making, ultimately contributing to safer and more effective treatments for patients.

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