VALIDATION OF A COGNITIVE SAFETY MONITORING SYSTEM FOR REAL TIME DETECTION OF CENTRAL NERVOUS SYSTEM ADVERSE EVENTS IN ALZHEIMER'S DISEASE CLINICAL TRIALS

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Background

In clinical trials of experimental drugs designed for the treatment of Alzheimer's disease (AD), some individual subjects may show an adverse reaction to the drug, and this can manifest as an encephalopathy, delirium, or exacerbation of dementia. Each of these conditions is characterized by an acute and substantial decline in cognition. However, because cognitive decline is expected in AD, it is difficult to differentiate cognitive decline that reflects an acute drug-related adverse event from disease-related cognitive decline. The aim of this study was to evaluate a cognitive safety monitoring system to guide decisions about the presence of clinically important decline in cognition in an individual subject that may reflect an adverse effect of a study drug.

Method

Participants: 199 older adults (57% female, average age = 71.5 yrs, SD = 8yrs) with classified clinically with MCI or mild AD and positive amyloid PET scan, were enrolled in a natural history study cognition was assessed at baseline, and weeks 12, 24, 38 and 52 visits. Medica assessment at each visit confirmed that no subject showed an adverse CNS event throughout the study.

Cognitive tests: Three computerized tests were selected based on their demonstrated stability in AD dementia, sensitivity to acute drug-related cognitive decline, and together required <10 minutes for administration. All tests had been administered in person by trained raters (Table 1).

Table 1: Cognitive tests used in the Cognitive Safety Monitoring System

Test	Domain	Outcome	Description
Detection	Information processing	Log10 milli-seconds	Speed of performance; mean of the $\log_{10}$ transformed reaction times
Identification	Attention	Log10 milli-seconds	Speed of performance; mean of the $\log_{10}$ transformed reaction times
International Shopping List Test (ISLT)	Verbal List Learning	N correct words from three trials	Number of words recalled correctly across the three learning trials of the ISLT (n)

Data analysis: Group mean change from baseline scores were computed for each cognitive test for each subject (Table 2). For each subject change from the immediately previous visit was computed and expressed as a reliable change index (RCI). The RCI for each test for each subject was computed as;

$$RCI = \frac{(x_2 - x_1)}{\sqrt{2} * WSD} * Multiplicand$$

Where:
x_1 = subject's baseline score
x_2 = subject's current score *(post-baseline)*
WSD = Within-Subject Standard Deviation
Multiplicand = -1 when the test primary outcome involves speed (*e.g., DET, IDN*

Group mean RCIs (for change from immediately previous visit) were computed for each test. Abnormal decline in performance was defined as a change of 1 WSD unit. Clinically important cognitive decline was defined when change occurred on 2 or more of the 3 tests to provide a familywise error of <5% for each comparison.

Results

Data analysis: For each cognitive test, baseline performance and change from immediately previously visit was computed. The WSD was the derived from the total model and multiplied by SQRT 2 (Table 2). For each subject, RCIs were computed with the frequency of abnormal decline in performance was computed

Table 2: AD group mean (SD) baseline and change from immediate visit

Visit	Detection M (SD)	Identification M (SD)	ISLT M (SD)
Baseline	2.60 (0.15)	2.80 (0.10)	13.02 (4.65)
Change to Week 12	0.00 (0.12)	0.00 (0.07)	0.39 (3.36)
Change to Week 24	-0.01 (0.11)	-0.01 (0.08)	0.27 (4.03)
Change to Week 38	-0.02 (0.13)	-0.01 (0.08)	0.86 (3.58)
Change to Week 52	-0.04 (0.13)	-0.03 (0.11)	1.48 (4.01)
Modelled WSD * SQRT2	0.113	0.113	5.67

To examine the frequency with which clinically important cognitive decline was classified as each post-baseline visit,

Table 3: Proportion of AD group classified with abnormal performance decline on the three cognitive test on each post-baseline visit

	n (%) of group with RCI ≤ -1.00 relative to previous assessment [abnormal decline in performance]			
No. of Tests	**Week 12 N=199**	**Week 24 N=197**	**Week 38 N=191**	**Week 52 N=184**
0	152 (76.1%)	155 (78.7%)	137 (71.7%)	136 (73.9%)
1	39 (19.6%)	37 (18.8%)	46 (24.1%)	38 (20.7%)
2	**8 (4.0%)**	**5 (2.5%)**	**8 (4.2%)**	**8 (4.3%)**
3	**0**	**0**	**0**	**2 (1.1%)**

Inspection of the rates of classification of abnormal performance decline in Table 3 shows that for the majority of subjects this did not occur at all.

Table 3 (dark blue numbers) shows that if a classification of clinically important cognitive decline required that a subject show abnormal performance decline on two or more of the three tests, then the rate of classification in this group as <5% for each post-baseline visit. A requirement of abnormal performance decline on the three tests classified 1% or less of subjects on any visit.

Conclusions

In patients with AD monitored for one year, for whom there was no acute CNS adverse events, performance on the tests in the Cognitive Safety Monitoring System remained relatively stable from visit to visit. Abnormal performance decline was rare, and where this did occur it was detected with for a single test only. This decline most likely reflects error. Requiring abnormal decline on two or more tests provided acceptable false positive rates for classification of clinically important cognitive decline.