

DE NOVO CLASSIFICATION REQUEST FOR COGNIVUE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Computerized Cognitive Assessment Aid. The Computerized Cognitive Assessment Aid is a prescription device that uses an individual's score(s) on a battery of cognitive tasks to provide an interpretation of the current level of cognitive function. The Computerized Cognitive Assessment Aid is used only as an assessment aid to determine level of cognitive functioning for which there exists other valid methods of cognitive assessment and does not identify the presence or absence of clinical diagnoses. The Computerized Cognitive Assessment Aid is not intended as a stand-alone or adjunctive diagnostic device.

NEW REGULATION NUMBER: 882.1470

CLASSIFICATION: CLASS II

PRODUCT CODE: PKQ

BACKGROUND

DEVICE NAME: COGNIVUE

SUBMISSION NUMBER: DEN130033

DATE OF DE NOVO: JUNE 24, 2013

**CONTACT: CEREBRAL ASSESSMENT SYSTEMS, INC.
CHARLES J. DUFFY, MD, PHD, FOUNDER AND CEO
2850 CLOVER STREET
PITTSFORD, NY 14534**

REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE

Cognivue testing is indicated as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55-95 years old.

LIMITATIONS

For prescription use only.

The safety and effectiveness of the Cognivue for individuals with less than 12 years of education has not been established.

The Cognivue is intended be used by medical professionals qualified to interpret the results of a cognitive assessment examination.

The device is not intended to be used as a stand-alone diagnostic device.

The device is not intended to identify the presence or absence of clinical diagnoses.

DEVICE DESCRIPTION

Cognivue provides clinicians in a healthcare setting with objective measurements of cognitive function as a screening aid in the assessment of adults 55 years of age and older. This is done for the purpose of identifying a potential decline in cognitive function relative to baseline test performance of other age-normal adults, referring those adults for further testing where warranted, and monitoring changes in cognitive function over time.

Cognivue presents a series of visual stimuli and a wedge-shaped cursor. The display presents stimuli at varying signal strengths with a moving domain-specific target. The patient identifies the target location by moving the cursor using the rotatory mouse manipulandum. The patient is scored based on the timing and accuracy of the responses. Repeated trials of varying difficulty characterize the subject's performance in each of the tested functional domains.

Cognivue Hardware Components:

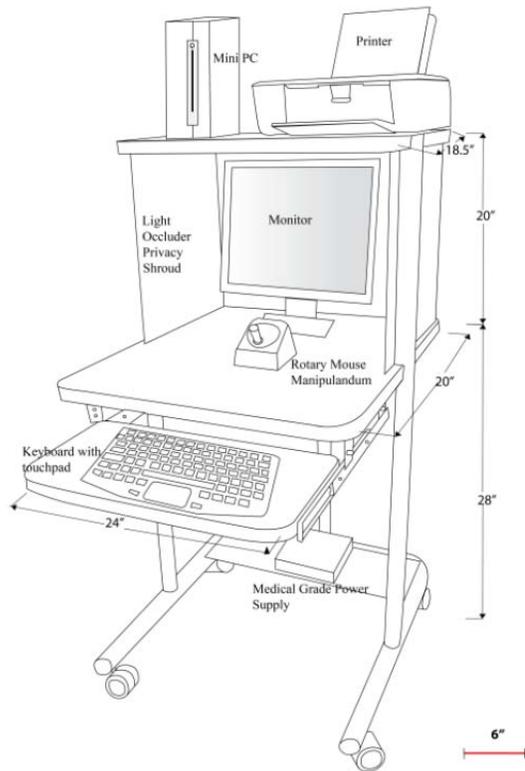
- Commercially available 4-wheel cart with seated height table top, slide-out keyboard tray, upper shelf, and lower shelf
- Plastic sheet connected to cart upright posts to enclose table-top testing area
- Commercially available printer adhered to upper shelf
- Commercially available mini-pc adhered to upper shelf
- Commercially available LCD flat screen display adhered to table top
- Rotatory mouse manipulandum adhered to cart table top for patient input
- Commercially available, wet/dry keyboard with integrated touch pad, located on slide-out keyboard tray.
- Commercially available, power supply adhered to lower shelf
- Commercially available power and interconnection cables

Cognivue Software Components:

- Software to support the graphical user interface (GUI)
- Software to interface with the rotatory mouse manipulandum
- Software to administer a battery of motor, visual, perceptual and memory tests (an overview of which is provided below)
- Software to support real-time test report generation, printing, and archiving

The Cognivue device computer, monitor, rotatory manipulandum, printer and mouse/keyboard are built from commercially available components and do not incorporate any unique materials other than those typical of desktop computers (Figure 1). The Cognivue cart is built out of steel, with four attached casters to provide stable mobility, and two shelves made of industrial-grade, laminated particle board. The monitor shroud is fabricated from a rigid non-translucent material secured to the cart. The Cognivue device cart, mini-pc, display screen, and printer do not incorporate any unique or proprietary materials. The Cognivue software is pre-installed.

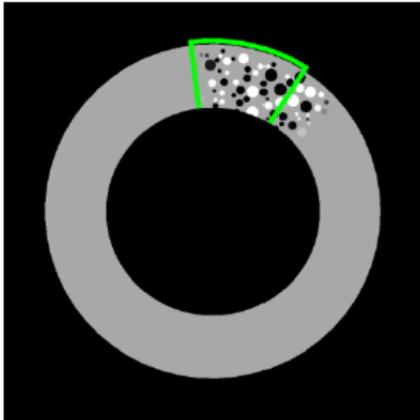
Figure 1. Cognivue Components



CAS's Cognivue technology enables the automated characterization of aspects of the perceptual and memory functions linked to human cortical information processing. Cognivue uses software running on a personal computer. The results are used to detect brain functional impairments in older adults (ages 55-95). This is accomplished by recording the subject's ability to respond to ten variations of visual stimuli. In all ten tests, the patient tracks the movement of a cursor-width target wedge (pie slice depicted in Figure 2) in a circular display by using a hand controller (rotatory manipulandum) to place the green cursor over the target wedge.

The CAS Cognivue test is rapid (~10 mins), extensive (including many brain functional domains), and non-invasive (patient contact only is made by the manipulandum).

Figure 2. Target Wedge Screen Example



Cognivue presents ten brain function tests in ten minutes. The battery is organized into three sub-batteries, with each sub-test preceded by transitional guidance that facilitates the test subject's engagement with minimal supervision:

Transitional guidance and textual instructions are presented at the start of each subtest, as described below:

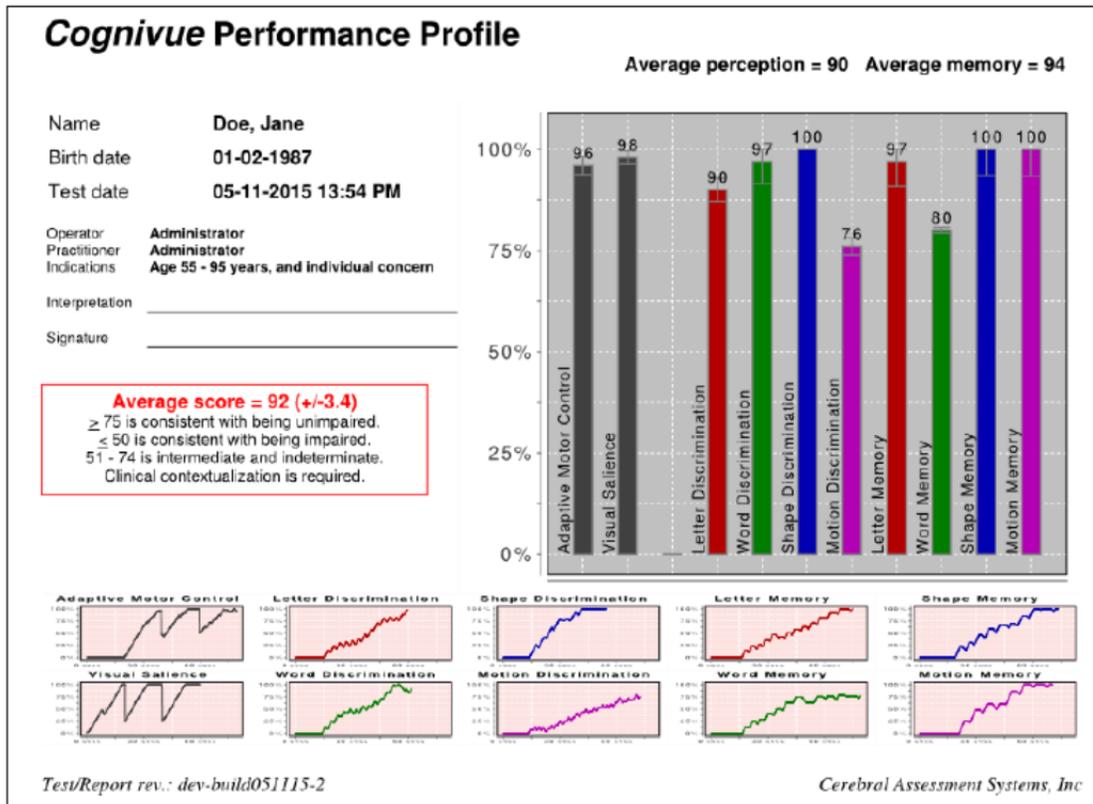
- Sub-Battery A: Two tests that measure adaptive motor control and dynamic visual contrast sensitivity, the results being used to adjust the remaining sub-tests to the basic response characteristics of the subject.
 - Adaptive Motor Control: Patient must follow a series of dots as they move around the circle and change direction and speed.
 - Visual Saliency Testing: Dots from previous test begin to fade (decreasing contrast) as the subject tracks them around the circle, while changing speed and direction.
- Sub-Battery B: Four perceptual tests measuring letter, word, shape, and motion processing ability:
 - Letter discrimination. Subject must correctly identify a real English letter.
 - Word discrimination. Subject must correctly identify a real English word.
 - Shape discrimination. Subject must correctly identify which shape is different.
 - Motion discrimination. Subject must identify which dot pattern is different.
- Sub-Battery C: Four memory tests measuring:
 - Letter memory. Subject must remember what letter was shown as a pre-cue, and identify that letter when presented in a circle populated with other letters.
 - Word memory. Subject must remember what word was shown as a pre-cue, and identify that word when presented in a circle populated with other words.
 - Shape memory. Subject must remember what shape was shown as a pre-cue, and identify that shape when presented in a circle populated with other shapes.

- Motion memory. Subject must remember what direction of motion was shown as a pre-cue, and identify that direction when presented in a circle populated with other directions.

Cognivue was validated against the St. Louis Mental Status (SLUMS) examination. The SLUMS is a cognitive screening tool which detects early cognitive problems, specifically mild cognitive impairment that is often missed by other mental status screening tools. The SLUMS is a psychometric scale with validated cut-off scores based upon the subject's education level. SLUMS scores are classified as: If subject is a high school graduate: >26 is unimpaired, <21 is impaired, others are intermediate. If subject is not a high school graduate: >24 is unimpaired, <20 is impaired, others are intermediate.

The Cognivue device output which yields a single output measure that is an average score of the four perception scores and four memory scores as depicted in Figure 3:

Figure 3. Sample Cognivue Output



Cognivue scores are classified as:

<p style="text-align: center;">Average Score = XX</p> <p>≥ 75 is consistent with being unimpaired. ≤ 50 is consistent with being impaired. 51 – 74 is intermediate and indeterminate. Clinical contextualization is required.</p>
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BIOCOMPATIBILITY/MATERIALS

Based on the device function and the recommendations of ISO 10993-1:2003, there is no biocompatibility testing required for this device.

Human test subject contact with the device is limited to their finger grasp of the three inch long plastic, non-conductive, disinfectant compatible handle on the rotatory mouse manipulandum. The handle is used much like pens or pencils in regular clerical applications, including such uses by patients in completing forms in doctors' offices. The handle part has undergone testing as part of the IEC 60601 certification testing by CSA, Inc. and has been found to comply with the FDA type BF classification and is labeled as such on the device and in the accompanying manuals.

Per the device certification documentation, there is no electrical continuity with the handle. If affected by spillage or other irregular exposure, the handle can be cleaned with regularly available contact disinfectant wipes.

SHELF LIFE/STERILITY

The CAS Cognivue testing system is not intended for use in any sterile application. It is not to be placed in any location within a sterile environment. It is not to be used by any individual who is maintaining, entering, or contacting any sterile field. Based on the device function there is no sterilization testing required for this device.

The CAS Cognivue testing system does not exhibit shelf life decay related to biomedical applications. The useful life of the device is limited by the years of expected life of computer components. Based on the device function there is no shelf-life limit applicable to the use of this device.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

Electrical safety testing was performed by Canadian Standards Association. The sponsor provides a letter of attestation stating the device passed IEC 60601-1:2005. Electromagnetic compatibility was not tested.

SOFTWARE

Version: Cognivue 3 RC20		
Level of Concern: MODERATE		
	Yes	No
Software description:	X	
Device Hazard Analysis:	X	
Software Requirements Specifications:	X	
Architecture Design Chart:	X	
Design Specifications:	X	
Traceability Analysis/Matrix:	X	
Development:	X	
Verification & Validation Testing:	X	
Revision level history:	X	
Unresolved anomalies:	X	

The operating system will be Ubuntu 12.04 release. The sponsor clarified that the software version is Cognivue 3.0 RC20 and that all new clinical validation testing was performed using this version. All previously unresolved anomalies were resolved and there are now no unresolved anomalies and the revision level history is provided.

The computer system has no network connectivity and data are not transmitted over a network (e.g., wireless, Ethernet, etc.). Patient data is exported onto USB drives and is encrypted using the Blowfish protocol.

PERFORMANCE TESTING – BENCH

The CAS Cognivue testing system is not bench tested as there are no existing bench standards for psychophysical testing in aging that would serve as a relevant comparison.

SUMMARY OF CLINICAL INFORMATION

The Sponsor provided a summary of testing conducted to demonstrate how the device functions as an interpretation of the current level of cognitive function. The summary of testing includes the following: The sponsor conducted two separate studies. The first study was conducted to determine the cut-off values for Cognivue (e.g., impaired, intermediate, and unimpaired cognitive function) by comparing the performance of Cognivue against a reference standard, the St. Louis University Mental Status (SLUMS) Examination. The second study was a clinical validation study which examined the agreement between the Cognivue classifications and the SLUMS classifications. The clinical validation study also examined the test – retest reliability study of Cognivue, and the determination of the construct validity of Cognivue via comparison with traditional paper and pencil neuropsychological tests.

A summary of the clinical validation study conducted included the following:

1. Study objective. The objective of this study was to demonstrate the safety and effectiveness of Cognivue as an adjunctive tool to be used by licensed practitioners evaluating brain function in adults aged 55 to 95 years old.
2. Clinical Study Design. The sponsor conducted a comparative study, using a paired design in which each subject undergoes blinded testing by separate testers administering Cognivue and a battery of non-reference standard tests, as per the FDA feedback. Test-retest reliability of both Cognivue and the reference standard, the St. Louis University Mental Status (SLUMS) Examination was conducted following a one to two week interval after initial testing.
3. Study/endpoints:
 - a. Cognivue agrees with the non-reference standard, SLUMS, in identifying unimpaired and impaired test subjects.
 - b. Cognivue shows test-retest reliability comparable to that of the SLUMS.
4. Study population. 401 subjects were enrolled at 13 older adult independent living communities. These sites consist of senior independent living facilities and an adult program for independent living seniors who are living at home. These sites enroll clients 55-95 years of age and who are cared for by primary care practitioners. Subjects were stratified in to three roughly equal groups, based on SLUMS scores:
 - a. Normal (SLUMS 27-30 if with high school education, and 25-30 if less than high school education),
 - b. Mildly impaired (SLUMS 21-26 if with high school education, and 20-24 if less than high school education),
 - c. Impaired (SLUMS 10-20 if with high school education, and 10-19 if less than high school education).
5. Test protocol:
 - a. Recruitment of subjects satisfying eligibility criteria.
 - b. Consent, consent related testing, and questionnaire by Tester #1 at the subject's test site.
 - c. Demographics and Indications for Use questionnaire by Tester #1.
 - d. Tester #1 administration of Cognivue v3 followed by,
 - e. Tester #2 administration of the neuropsychological test battery.
 - f. Repeat steps a – e (above) in same subjects after one to three weeks.
6. Study procedures. The SLUMS classification of all study subjects were compared with the classification produced by the Cognivue v3 average score (mean of 4 perception and 4 memory scores). Cognivue classification is derived using a Cognivue score of ≤ 50 to identify impaired subjects, a Cognivue score of ≥ 75 to identify unimpaired subjects, and identifying as intermediate all subjects who score between those values. These high and low cut-off values for the final average Cognivue score are derived from a preliminary study of 92 subjects as a separate sample from the study population who were tested with

Cognivue v3 and SLUMs.

Subjects had Cognivue and neuropsychological testing in two sessions 1-2 weeks apart without feedback, minimizing learning effects. Neuropsychological testing consisted of:

1. SLUMS
 2. Separate scoring of SLUMS Clock Drawing
 3. Separate scoring SLUMS Animal Naming
 4. Rey Auditory Verbal Learning Test
 5. Trail Making Test – Parts A and B
 6. Benton Judgment of Line Orientation
 7. Figural Memory
 8. The Purdue Peg Board
 9. Hamilton-Veale Contrast Sensitivity
 10. Geriatric Depression Scale (15 item version).
7. Eligibility criteria:
- a. Inclusion criteria: Men and women 55-95 years old.
 - b. Exclusion criteria:
 - i. Impaired vision of both eyes as judged by poor contrast sensitivity (quantified by Hamilton-Veale Contrast Sensitivity < 7)
 - ii. Impaired manual dexterity of both hands as judged by timed performance below cut-off standards for the left and the right hands (quantified by Purdue Peg Board scores < 6).
 - iii. Ineligible for written informed consent as judged by >4 errors in reading the introductory paragraph of the consent form aloud while holding the text at the most comfortable viewing distance (typically 12-18”, printed in Gulim sans serif, size 14, character spacing expanded by 1 point and line spacing printed at 1.5) while wearing their customary corrective lenses. The text is as follows:
“This consent form describes what to expect if you decide to take part in this study. Please listen carefully as the consent form is read to you. Ask any questions you have before deciding to take part. We suggest that you use the bathroom before the testing begins.”
 - iv. Inability to answer three questions about testing after consent is read to the subject:
 1. How long does each session take? (Correct response is fewer than 90 mins per session.)
 2. How many sessions are there? (Correct response is a total of two sessions.)
 3. How much will you be getting paid? (Correct response is twenty dollars per session.)

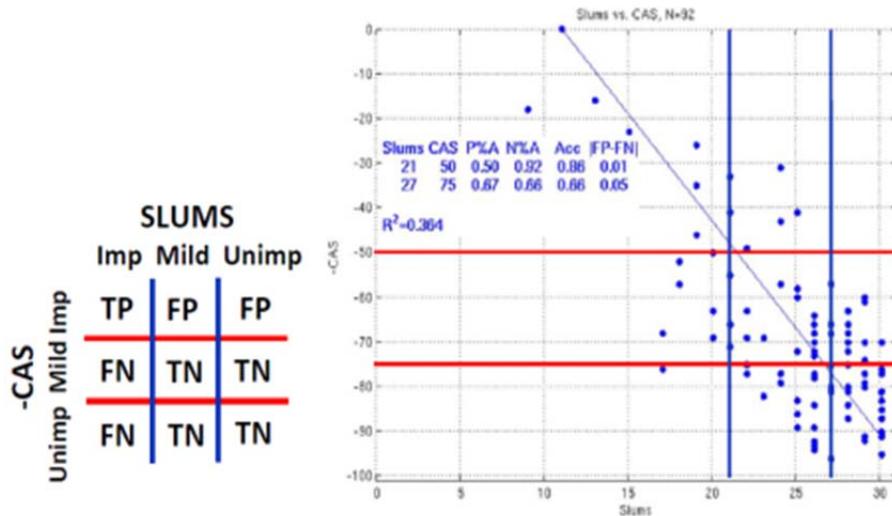
8. Clinical Performance Results.

- a. Cognivue Cut-Offs Analysis. Scores on Cognivue and the SLUMS were compared in a sample of assisted and independent living adults, ages 55-95 years old, to find Cognivue scores that yield correspondence with SLUMS patient classification as: impaired, unimpaired, and intermediate. The data obtained from 92 subjects were utilized to determine the cut-off data. SLUMS scores ranged from 0 – 30 and classified as: >26 unimpaired, <21 is impaired, intermediate scores are classified as mild impairment.

Two optimization methods were conducted to determine the cut-off values for Cognivue scores. In the first method, the sponsor optimized the PPA and NPA. Specifically, on each of the two cut-off values for SLUMS score (< 21 or >=27), the sponsor obtained the cut-off values for Cognivue scores that minimize the objective function. In the second method, the sponsor repeated the same procedure but optimized another objective function, where 1-ACC is inaccuracy, $(1 - [TP + TN]/total)$ and BGI is error bias (contrast ratio [difference/sum] of FPs & FNs).

The results from these analyses indicated that Cognivue scores ≤ 50 are consistent with a conservative standard for impairment and that Cognivue scores ≥ 75 are consistent with a conservative standard for un-impairment. Scores between 50 and 75 represent an intermediate result that has no significance.

The scatter plot representing the scores for the 92 subjects in the Cut-Offs Study:



The table to the left of the scatter plot is a key for relating the plot to subject classification. The table enclosed in the scatter plot shows the results of analyses of classification:

Top Line: Impairment cut-off values of SLUMS ≥ 21 ; Cognivue ≥ 50 yield the following:

Negative Percent Agreement (NPA, $100 \times [TP/TP+FP]$) = 50
Positive Percent Agreement (PPA, $100 \times [TP/TP+FP]$) = 86
Accuracy (ACC, $[True\ Positives + True\ Negatives]/total\ sample$) = .86
Error Symmetry ($[False\ Positives - False\ Negatives]/total$) = .01.

Bottom Line: Unimpaired cut-off values of SLUMS ≥ 27 and Cognivue ≥ 75 yield the following:

Negative Percent Agreement (NPA, $100 \times [TP/TP+FP]$) = 67
Positive Percent Agreement (PPA, $100 \times [TP/TP+FP]$) = 66
Accuracy (ACC, $[True\ Positives + True\ Negatives]/total\ sample$) = .66
Error Symmetry ($[False\ Positives - False\ Negatives]/total$) = .05.

Summary: Cognivue cut-off scores between 55 and 64 provide an acceptable adjunctive tool for recognizing patients who would score 0-20 on SLUMS, a range of SLUMS scores that suggests the presence of impairment. Cognivue cut-off scores between 74 and 79 provide an acceptable adjunctive tool for recognizing patients who would score 27-30 on SLUMS, a range of SLUMS scores that suggests the absence of impairment. Cognivue scores between the impairment and unimpairment ranges described above would provide an acceptable adjunctive tool for recognizing patients who should score 21-26 on SLUMS, a range of SLUMS scores that suggests an intermediate condition between the presence and absence of impairment.

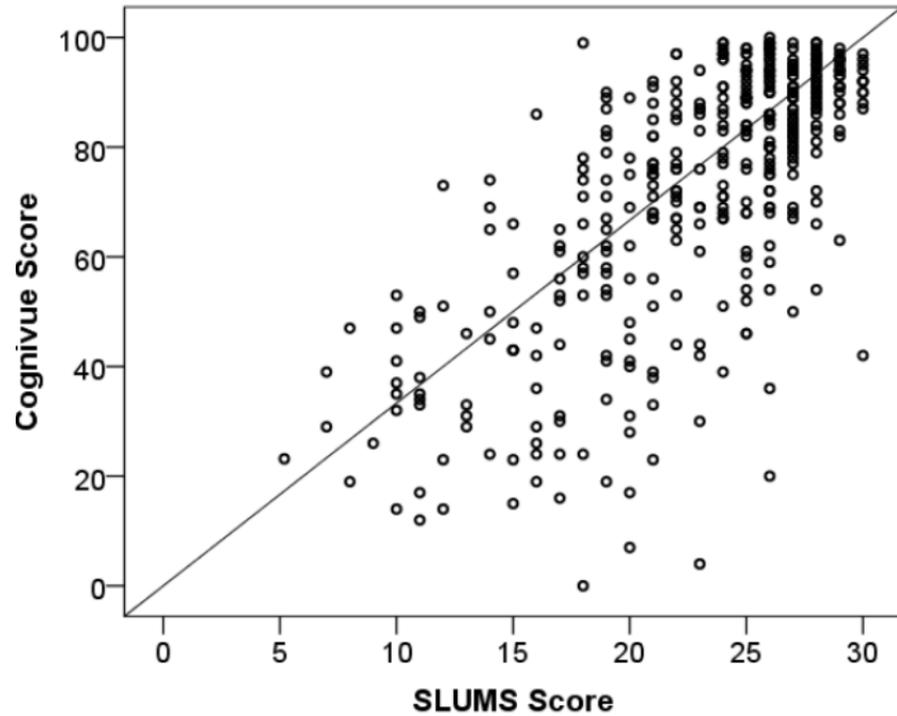
Cognivue scores ≤ 50 are consistent with a conservative standard for impairment. That is, an impairment standard that avoids errors in which Cognivue might imprudently support the impression that a patient is impaired. Cognivue scores ≥ 75 are consistent with a conservative standard for unimpairment. That is, an unimpairment standard that avoids errors in which Cognivue might imprudently support the impression that a patient is not unimpaired.

- b. *Agreement analyses (SLUMS and Cognivue).* This analysis was an agreement analysis between the subject device, Cognivue score (range from 0-100), and the non-reference standard, the St. Louis University Mental Status Examination (SLUMS, range from 0-30). The sponsor also did the agreement analysis on the classification results of Cognivue and SLUMS, impaired, unimpaired, and intermediate. The data obtained from the first test session of 401 subjects was utilized to determine the agreement between SLUMS and Cognivue. Subjects were classified as follows:
- *SLUMS:* SLUMS scores are classified as: If subject is a high school graduate: >26 is unimpaired, <21 is impaired, others are intermediate. If subject is not a high school graduate: >24 is unimpaired, <20 is impaired, others are intermediate

- *Cognivue*: Cognivue scores are classified as: >74 is unimpaired, <51 is impaired, scores of 50 – 75 are intermediate.

i. Regression Analyses:

1. Scatterplot of SLUMS (abscissa, full-scale 0-30) and Cognivue (ordinate, full-scale 0-100) co-plotted with 45 degree line in Excel:



Deming regression (unweighted) calculated in Analyse-it yields the line:

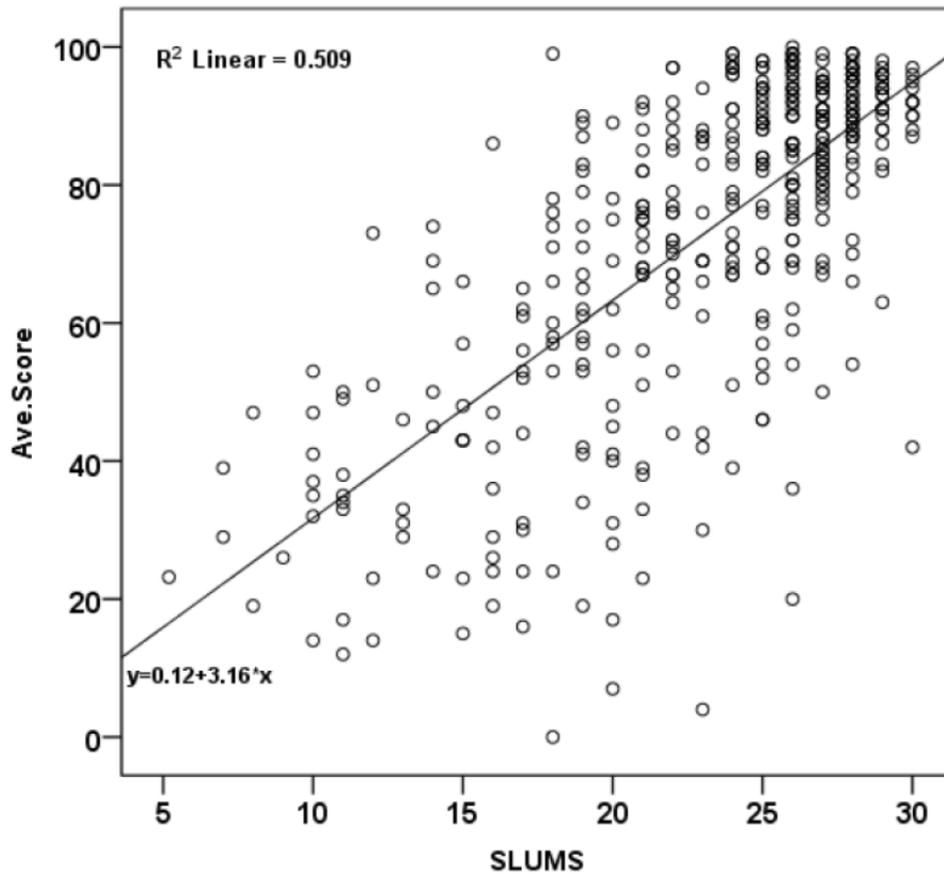
$$\text{Cognivue} = -29.98 + 4.465 \text{ SLUMS}$$

Intercept 95% CI = -42.52 to -17.44, SE = 6.3790, $p < .0001$

Slope 95% CI = 3.966 to 4.964, SE = .254, $p < .0001$

$r = 0.71$.

2. Linear regression:



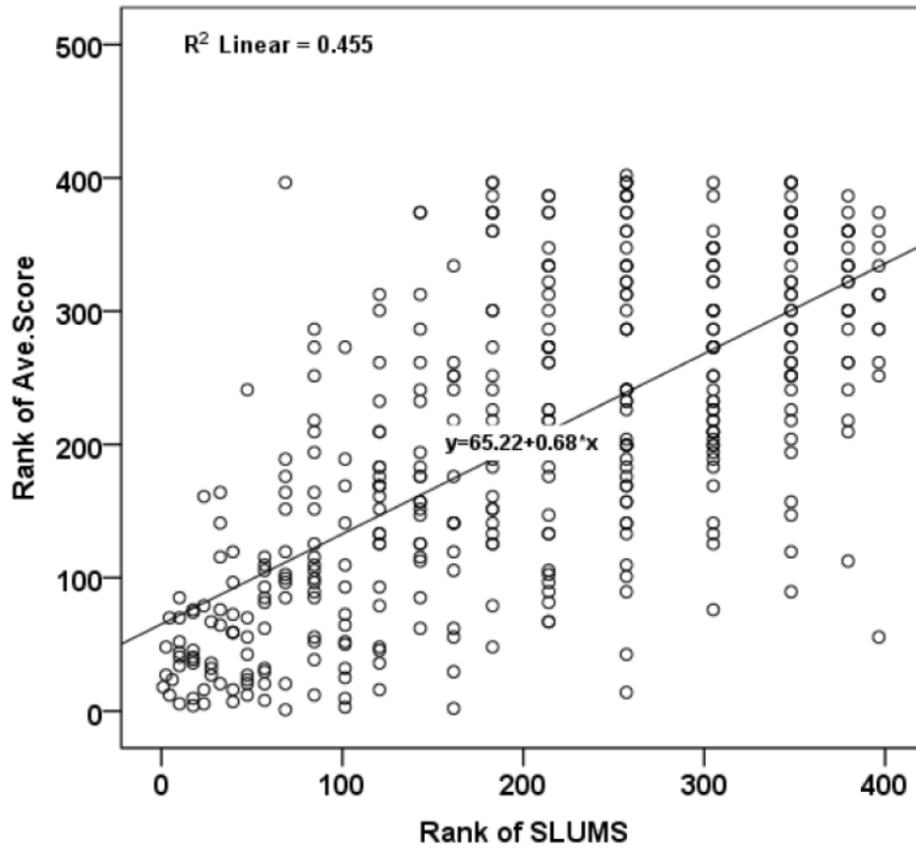
Cognivue Avg. Score = 0.12 + 3.16 SLUMS

Intercept 95% CI = -7.06 to 7.31, SE = 3.66, p<.001

Slope 95% CI = 2.85 to 3.46, SE = .155, p<.001

r = 0.71.

3. Rank linear regression:



Cognivue Avg. Score Rank = 65.22.98 + 0.68 SLUMS
 Intercept 95% CI = 48.31 to 82.14, SE = 8.604, p<.001
 Slope 95% CI = 0.604 to 0.749, SE = 0.037, p<.001
 r = 0.68.

ii. Agreement analysis:

		SLUMS			
<i>Cognivue</i>		Impaired	Intermediate	Unimpaired	Total
	Impaired	a 60	b 14	c 2	76
	Intermediate	d 34	e 46	f 8	88
	Unimpaired	g 13	h 114	i 110	237
	Total	107	174	120	401

Including the SLUMS intermediate scores grouped with unimpaired scores:
 PPA = 100% X a / (a + d + g)

$$\text{PPA} = 100\% \times 60 / (60 + 34 + 13) = 56\%$$

(95% Wilson interval: .47 to .65)

$$\text{NPA} = 100\% \times (e + f + h + i) / (b + c + e + f + h + i)$$

$$\text{NPA} = 100\% \times (46 + 8 + 114 + 110) / (14 + 2 + 46 + 8 + 114 + 110) = 95\%$$

(95% Wilson interval: .91 to .97)

A quadratic weighted kappa score derived in *Analyse-it* = .57 (Wald 95% CI .50 to .63). This suggests a clear categorical relationship between *Cognivue* and SLUMS outcomes.

Omitting all intermediate groups as being in an indeterminate condition, a condition about which no firm conclusion is clinically justified, the data yield:

$$\text{PPA} = 100\% \times 60 / (60 + 13) = 82\%$$

(95% Wilson interval: .72 to .89)

$$\text{NPA} = 100\% \times 110 / (2 + 110) = 98\%$$

(95% Wilson interval: .93 to .99)

This suggests a categorical relationship between *Cognivue* and SLUMS outcomes for patients who are either impaired or unimpaired.

Summary: These findings confirm agreement between SLUMS and *Cognivue*. *Cognivue* can inform an impression that a patient is unimpaired or is impaired. *Cognivue* sets a conservative standard for supporting the impression that a mildly impaired patient should be presumed to be impaired.

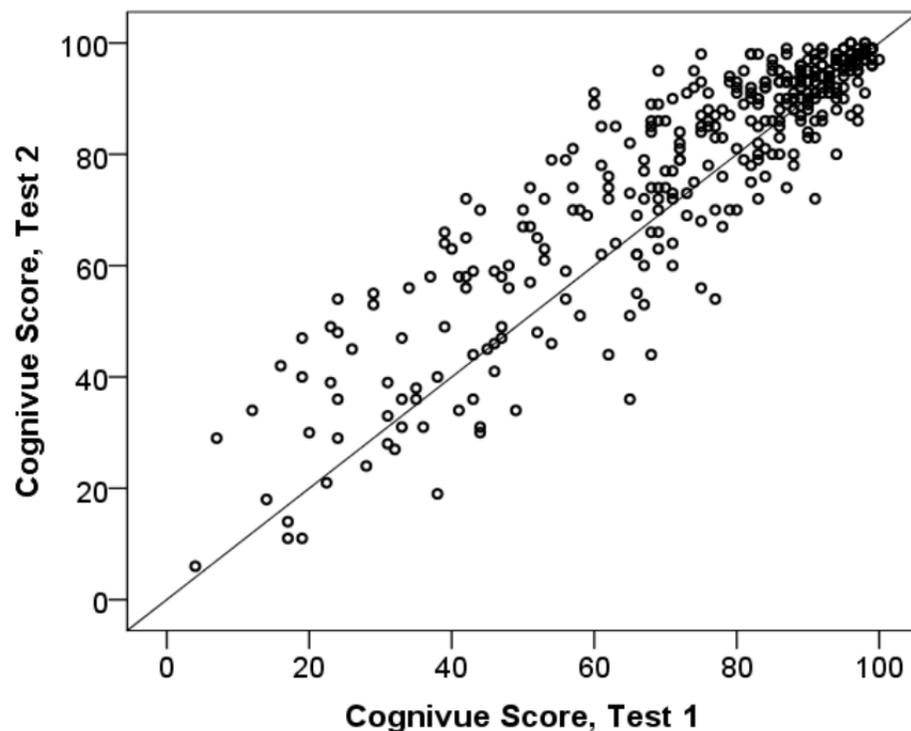
- c. *Analysis of the Test-Retest Reliability of Cognivue Classification and SLUMS Scores.* The purpose of these analyses was to compare scores from the repeated administration of *Cognivue*, and from the repeated administration of SLUMS, to assess the re-test reliability of *Cognivue*, and to compare the re-test reliability of *Cognivue* to the re-test reliability of SLUMS. Subjects underwent *Cognivue* and SLUMS testing in two sessions 1-2 weeks apart without feedback, minimizing the impact of learning effects.

Cognivue and SLUMS subject classifications from the first and second tests are in 3 X 3 tables. Scatterplots are presented to represent data related to regression analyses. PPAs, NPAs assess test-retest reliability along with weighted kappa scores at a 95% CI. Changes in SLUMS (>3) and GDS scores (>2) will filter-out subjects who may show non-measurement re-test changes. Intraclass correlation coefficients describe relations between *Cognivue* and SLUMS scores, and their respective retest reliability using one-way random effects analyses of variance with subjects as the

random effect. Bland-Altman plots of the Day 2 – Day 1 difference (Y) vs. the mean over the 2 days (X) describe these findings.

The data obtained for the test-retest reliability analyses included 358 subjects reduced from 401 who were unavailable for repeat testing or among the last tested who could only be tested once due to deadline time constraint. The group of 43 subjects who were only tested once are those who did not sign-up for a second session within the period of testing at their site.

- i. Cognivue test-retest regression analysis. The following is the scatterplot of of Cognivue first test scores (abscissa, full-scale 0-100) and Cognivue second test scores (ordinate, full-scale 0-100) co-plotted with 45 degree line:

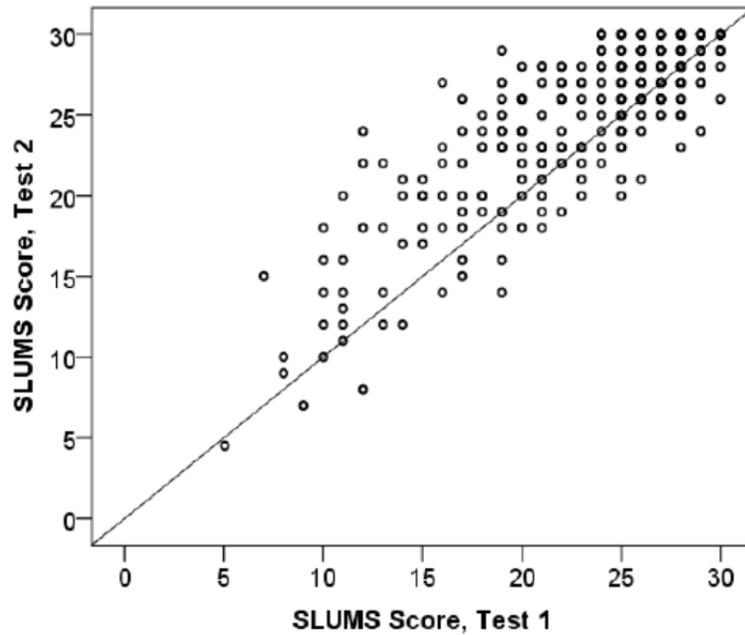


Deming regression (unweighted) calculated in Analyse-it yields the line:

$$\begin{aligned} \text{Cognivue 2} &= 9.06 + 0.936 \text{ Cognivue 1} \\ \text{Intercept 95\% CI} &= 4.27 \text{ to } 13.84, \text{ SE} = 2.433, p=.0002 \\ \text{Slope 95\% CI} &= 0.880 \text{ to } 0.993, \text{ SE} = 0.0285, p=.0264 \\ r &= 0.90. \end{aligned}$$

These findings demonstrate substantial and significant agreement between Cognivue first test and Cognivue second test scores.

- ii. SLUMS test-retest regression analysis. The following is a scatterplot of SLUMS first test scores (abscissa, full-scale 0-30) and SLUMS second test scores (ordinate, full-scale 0-30) co-plotted with 45 degree line:



Deming regression (unweighted) calculated in Analyse-it yields the line:
 $SLUMS\ 2 = 4.15 + 0.90\ SLUMS\ 1$
 Intercept 95% CI = 2.24 to 6.06, SE = 0.970, $p < .0001$
 Slope 95% CI = 0.82 to .97, SE = .039, $p = .039$
 $r = 0.82$.

These findings demonstrate substantial and significant agreement between SLUMS first test SLUMS second test scores.

- iii. Re-test Reliability Analysis on the Categorical *Cognivue* Classification. The results on the categorical *Cognivue* classifications, impaired, unimpaired, and intermediate as a 3×3 table are as follows:

		<i>Cognivue</i> 1st Test			
<i>Cognivue</i> 2nd Test		Impaired	Intermediate	Unimpaired	Total
	Impaired	a 42	b 21	c 0	63
	Intermediate	d 5	e 41	f 32	78
	Unimpaired	g 0	h 10	i 207	217
Total	47	72	239	358	

$$PPA = 100\% \times a / (a + d + g)$$

$$PPA = 100\% \times 42 / (42 + 5 + 0) = 89\%$$

(95% Wilson interval: .77 to .95)

$$\begin{aligned} \text{NPA} &= 100\% \times (e + f + h + i) / (b + c + e + f + h + i) \\ \text{NPA} &= 100\% \times (41 + 32 + 10 + 207) / (21 + 0 + 41 + 32 + 10 + 207) = \\ &93\% \\ &\text{(95\% Wilson interval: .90 to .96)} \end{aligned}$$

- iv. Re-test Reliability Analysis on the *SLUMS* classification. The analysis results on the categorical classification for the non-reference standard, *SLUMS* as a 3 x 3 table:

SLUMS 1st Test					
SLUMS 2nd Test		Impaired	Intermediate	Unimpaired	Total
	Impaired	a 48	b 35	c 5	88
	Intermediate	d 7	e 70	f 80	157
	Unimpaired	g 0	h 23	i 90	113
	Total	55	128	175	358

$$\begin{aligned} \text{PPA} &= 100\% \times a / (a + d + g) \\ \text{PPA} &= 100\% \times 48 / (48 + 7 + 0) = 87\% \\ &\text{(95\% Wilson interval: .76 to .94)} \end{aligned}$$

$$\begin{aligned} \text{NPA} &= 100\% \times (e + f + h + i) / (b + c + e + f + h + i) \\ \text{NPA} &= 100\% \times (70 + 80 + 23 + 90) / (35 + 5 + 70 + 80 + 23 + 90) = 87\% \\ &\text{(95\% Wilson interval: .83 to .90)} \end{aligned}$$

- v. Percent Agreement for *Cognivue* Cut-Points (Three Categories):

Cognivue 1st Test					
Cognivue 2nd Test		Impaired	Mildly Impaired	Unimpaired	Total
	Impaired	a 42	b 21	c 0	63
	Mildly Impaired	d 5	e 41	f 32	78
	Unimpaired	g 0	h 10	i 207	217
	Total	47	72	239	358

$$\text{Percent agreement for impaired: tests 1 and 2} = 100.0\% * 42 / (42 + 5 + 0) = 89\%$$

$$\text{Percent agreement for mildly impaired: tests 1 and 2} = 100.0\% * 41 / (21 + 41 + 10) = 57\%$$

Percent agreement for unimpaired: tests 1 and 2 = $100.0\% * 207/(0+32+207)$
 = 87%

vi. Percent Agreement for *SLUMS* Cut-Points (Three Categories):

SLUMS 1st Test					
SLUMS 2nd Test		Impaired	Mildly Impaired	Unimpaired	Total
	Impaired	a 48	b 35	c 5	88
	Mildly Impaired	d 7	e 70	f 80	157
	Unimpaired	g 0	h 23	i 90	113
	Total	55	128	175	358

Percent agreement for impaired: tests 1 and 2 = $100.0\% * 48/(48+7+0)$ = 87%

Percent agreement for mildly impaired: tests 1 and 2 = $100.0\% * 70/(35+70+23)$ = 55%

Percent agreement for unimpaired: tests 1 and 2 = $100.0\% * 90/(5+80+90)$ = 51%

vii. Impairment Classification Agreement for *Cognivue* Test 1 to Test 2:

	Impaired	Mildly Impaired	Unimpaired	Total
<i>Cognivue 1</i>	47	72	239	358
<i>Cognivue 2</i>	63	78	217	358
Total	110	150	456	716

The Fisher-Freeman-Halton exact test (SPSS v22) yields a value of 3.62 (df = 2), $p = 0.161$. The *Cognivue* classifications for impairment, mild impairment, and unimpairment do not differ significantly by the time of the test in the tested population.

viii. Impairment Classification Agreement for *SLUMS* Test 1 to Test 2:

	Impaired	Mildly Impaired	Unimpaired	Total
SLUMS 1	55	128	175	358
SLUMS 2	88	157	113	358
Total	143	285	288	716

The Fisher-Freeman-Halton exact test (SPSS v22) yields a value of 24.89 (df = 2), $p < 0.001$. The SLUMS classifications for impairment, mild impairment, and unimpairment differ significantly by the time of the test in the tested population.

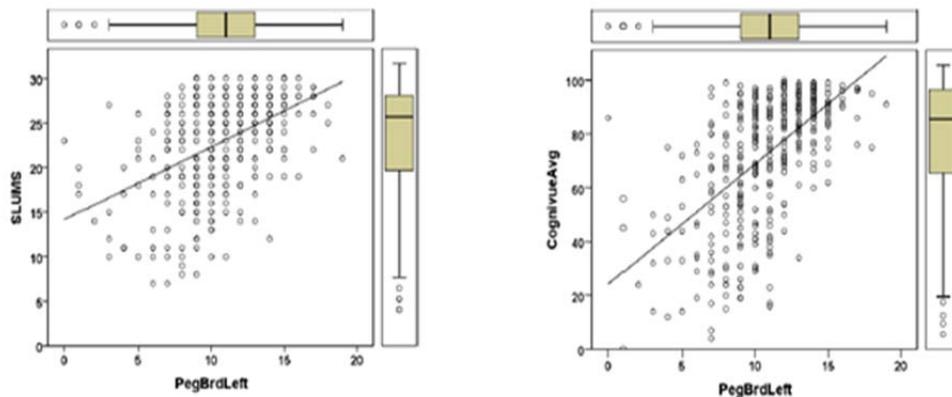
- d. *Psychometric Validation of the Cognivue Test Battery*. The goal of this analysis was to compare scores from the repeated administration of Cognivue, and from the repeated administration of a battery of neuropsychological tests, to characterize the psychometric properties of Cognivue and to compare those properties to that of SLUMS. The data obtained from 401 subjects was used for these analyses. The Pearson correlations were obtained for bivariate comparisons of SLUMS scores and neuropsychological test scores and for Cognivue scores and neuropsychological test scores run in SPSS v12 Correlation Analysis which yielded the following results:

Correlations		SLUMS	Cognivue Avg
SLUMS	Pearson Correlation		.710
	Sig. (2-tailed)		.000
	N		401
Cognivue Avg	Pearson Correlation	.710	
	Sig. (2-tailed)	.000	
	N	401	
PegBrdLeft	Pearson Correlation	.485	.597
	Sig. (2-tailed)	.000	.000
	N	401	401
PegBrdRight	Pearson Correlation	.522	.589
	Sig. (2-tailed)	.000	.000
	N	401	401
PegBrdBiManual	Pearson Correlation	.506	.600
	Sig. (2-tailed)	.000	.000
	N	401	401
ContrastLeft	Pearson Correlation	.255	.405
	Sig. (2-tailed)	.000	.000
	N	401	401
ContrastRight	Pearson Correlation	.284	.419
	Sig. (2-tailed)	.000	.000
	N	401	401
ContrastBinoc	Pearson Correlation	.297	.472
	Sig. (2-tailed)	.000	.000
	N	401	401
Animal_Name	Pearson Correlation	.665	.655
	Sig. (2-tailed)	.000	.000
	N	401	401
Clock_Draw	Pearson Correlation	.700	.580
	Sig. (2-tailed)	.000	.000
	N	401	401

Correlations		SLUMS	CognivueAvg
RAVLTA-1	Pearson Correlation	.513	.514
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTA-2	Pearson Correlation	.617	.597
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTA-3	Pearson Correlation	.605	.588
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTA-4	Pearson Correlation	.650	.616
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTA-5	Pearson Correlation	.651	.585
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTA-6	Pearson Correlation	.628	.539
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTA-7	Pearson Correlation	.617	.530
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLThits	Pearson Correlation	.522	.468
	Sig. (2-tailed)	.000	.000
	N	401	401
RAVLTFps	Pearson Correlation	-.287	-.255
	Sig. (2-tailed)	.000	.000
	N	401	401

Correlations			
		SLUMS	CognivueAvg
Figural_Memory	Pearson Correlation	.385	.408
	Sig. (2-tailed)	.000	.000
	N	401	401
JOLO	Pearson Correlation	.451	.487
	Sig. (2-tailed)	.000	.000
	N	400	400
TrailsATime	Pearson Correlation	-.448	-.566
	Sig. (2-tailed)	.000	.000
	N	401	401
TrailsAErrs	Pearson Correlation	-.242	-.282
	Sig. (2-tailed)	.000	.000
	N	401	401
TrailsBTime	Pearson Correlation	-.599	-.663
	Sig. (2-tailed)	.000	.000
	N	401	401
TrailsBErrs	Pearson Correlation	-.500	-.533
	Sig. (2-tailed)	.000	.000
	N	401	401
GDS	Pearson Correlation	-.312	-.248
	Sig. (2-tailed)	.000	.000
	N	401	401

In addition, scatterplots of the psychometric test scores (ordinates) and SLUMS scores (left column, abscissas) or Cognivue scores (right column abscissas) with axis quartile plots using SPSS v22. The sponsor provided over 50 scatter plots in DEN130033/S001. Below are representative examples of these plots:



These analyses show that both Cognivue scores and SLUMS scores are most closely correlated with three types of measures (ranking from Supplementary Analyses):

- Verbal processing (Animal Naming, and RAVLT),
- Visuospatial and executive function (Trails B and Clock Drawing)
- Manual dexterity and speed (Peg Board),
- Speed and sequencing (Trails A)
- Visual acuity (contrast sensitivity)

9. Conclusions. The sponsor conducted a validation study of their computerized cognitive assessment device that administers a battery of computerized cognitive tests of perceptual and memory function via the use of psychophysical assessment measures. The Cognivue validation study consisted of the following:
- Establishment of cut-off values for impaired, unimpaired, and intermediate ranges for the device.
 - Analysis of agreement between the Cognivue device and an established reference standard, The St. Louis University Mental Status (SLUMS) Examination.
 - Analysis of the test-retest reliability of both the Cognivue test results and the SLUMS test results
 - Psychometric validation of the Cognivue cognitive test battery via comparison to traditional paper and pencil neuropsychological tests.

The sponsor has conducted an appropriate validation study which yields an average score of the perceptual and memory test battery which establishes cut-off scores for the Cognivue device as follows:

<p style="text-align: center;">Average Score = XX</p> <p>≥ 75 is consistent with being unimpaired.</p> <p>≤ 50 is consistent with being impaired.</p> <p>51 – 74 is intermediate and indeterminate.</p> <p style="text-align: center;">Clinical contextualization is required.</p>

The validation study also demonstrated good agreement between Cognivue and SLUMS with regard to classifying subjects as impaired, unimpaired or intermediate. The reported positive percent agreement (PPA) of 56% included the intermediate range. The negative percent agreement (NPA) is much more robust at 95% and suggests that the Cognivue device has greater capacity for determining that a subject's cognitive function is not impaired. Scores in the intermediate range may or may not have significance and the recommendation for further clinical evaluation for subjects who score in the intermediate range is valid. Omitting all intermediate scores as being in an indeterminate condition, a condition about which no firm conclusion is clinically justified, the data yield stronger PPA.

Disagreement between Cognivue and SLUMS is attributable to subjects whom Cognivue test result classifies a subject as unimpaired and SLUMS scores who score in the intermediate classification of mildly impaired. These are subjects with SLUMS scores of 26, at the boundary of SLUMS unimpaired and mildly impaired categories.

The Cognivue device demonstrated acceptable test-retest reliability and was consistent with reliability coefficients obtained in traditional psychological and neuropsychological tests. In addition, the Cognivue classifications for impairment, mild impairment, and unimpairment do not differ significantly by the time of the test in the tested population.

The psychometric validation of the Cognivue test battery against traditional neuropsychological tests was adequate. The correlation coefficients between the specific

neuropsychological tests and both the Cognivue average score and the SLUMS score range from approximately 0.40 to 0.66 which are essentially within the acceptable ranges for determining construct validity for psychometric tests which have often have more variability due to a variety of factors (e.g., age, gender, level of education, etc.).

LABELING

The labeling for the Cognivue device consists of four manuals:

1. Quick Start Manual. The Cognivue Quick Start Guide is a short, two-page manual for operators of this device. It provides instructions for starting Cognivue, entering patient information, and instructing subjects on how to use the rotary manipulandum. The manual indicates this device is prescription use only.
2. Practitioner's Manual. The Practitioner's Manual is a detailed description for licensed health care providers regarding test interpretation. The labeling clearly states that the device is prescription use only and the results serve as an as an adjunctive tool to be integrated with other sources of information regarding a subject's condition and that clinical correlation is required. Warnings in the labeling include that Cognivue is not to be used as a stand-alone diagnostic and the result of Cognivue do not identify the presence or absence of clinical diagnoses. Detailed descriptions of each subtest from the Perceptual and Memory batteries are provided. The labeling states that no clinical interpretation can be drawn for scores in the intermediate range (e.g., 50 – 75). The Cognivue Practitioners' Manual provides four Appendices which contain the clinical performance data, including (1) development of the Cognivue cut-off scores, (2) clinical validation study results, (3) test – retest reliability result, and (4) psychometric characteristics of the Cognivue test battery (e.g., construct validity of the subtests).
3. Practitioner's Training Manual. The Practitioner's Training Manual consists of information regarding the development of the Cognivue cognitive test battery based upon psychophysical stimulus-response paradigms. The labeling clearly states that the device is prescription use only and the results serve as an as an adjunctive tool to be integrated with other sources of information regarding a subject's condition and that clinical correlation is required. In addition, this manual provides more detailed instructions for starting Cognivue, testing a subject, and providing subjects with instructions for completing each of the cognitive tasks.
4. Operator's Manual. The Operator's Manual provides detailed information regarding the hardware and software components of the Cognivue device, including general and electrical safety precautions and cleaning of the rotary manipulandum procedures. This manual also includes detailed instructions to individuals who will administer the Cognivue cognitive test battery to subjects.

SPECIAL CONDITIONS FOR USE

Cognivue interpretation guidelines are based upon the average score of the four perceptual battery tests and the four memory battery tests which yields a Total Average Score for interpretation of an individual's performance as impaired, intermediate, or unimpaired. In order

to use Cognivue, the user should be medical professionals with expertise in the assessment of cognitive disorders and must have familiarized themselves with all the manuals and labeling of Cognivue.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of Computerized Cognitive Assessment Aids and the measures necessary to mitigate these risks.

Identified Risk	Mitigation Measure
Equipment malfunction leading to subject injury (shock, burn, or mechanical failure)	Electrical safety testing Labeling
User discomfort (e.g., visual fatigue, stimulus-induced nausea)	Labeling
Incorrect result, inclusive of: <ul style="list-style-type: none"> • False positive – cognitive impairment when in fact none is present • False negative – cognitive impairment when in fact cognitive impairment is present 	Hardware and Software verification, validation and hazard analysis Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Computerized Cognitive Assessment Aid is subject to the following special controls:

1. The technical parameters of the device’s hardware and software must be fully characterized and be accompanied by appropriate non-clinical testing:
 - a. Hardware specifications must be provided. Appropriate verification, validation and hazard analysis must be performed.
 - b. Software, including any proprietary algorithm(s) used by the device to arrive at its interpretation of the patient’s cognitive function, must be described in detail in the Software Requirements Specification (SRS) and Software Design Specification (SDS). Appropriate software verification, validation, and hazard analysis must be performed.
2. The device must be designed and tested for electrical safety.
3. The labeling must include:
 - a. A summary of any testing conducted to demonstrate how the device functions as an interpretation of the current level of cognitive function. The summary of testing must include the following, if available: any expected or observed adverse events and complications; any performance measurements including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) per the device intended use; a description of the repeatability of measurements; a description of how the cut-off values for categorization of measurements were determined; and a description of the construct validity of the device.
 - b. A warning that the device does not identify the presence or absence of clinical diagnoses.

- c. A warning that the device is not a stand-alone diagnostic
- d. The intended use population and the intended use environment.
- e. Any instructions technicians must convey to patients regarding the administration of the test and collection of cognitive test data.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in the clinical validation study. There were no serious adverse events reported in the study. No adverse device events and no unanticipated device reports were reported. The risks to health are relatively minimal as computerized cognitive assessment batteries are considered a non-invasive medical device and the device does not provide a clinical diagnosis. The risk of a false positive result may result in result in the clinician conducting a more detailed and extensive medical work-up to determine if a subject actually has cognitive impairment that would not be expected for his/her age and educational level. The risk of a false negative result would also be considered minimal. Clinicians would still be responsible for conducting a diagnostic work-up for patients presenting with cognitive impairment symptoms regardless of the Cognivue device result.

The probable benefits of the device are based on data collected in the study as described above. Cognivue is an assessment aid consisting of a cognitive screening tool that allows the clinician to integrate the results of the cognitive assessment into their clinical decision making regarding the need for a further diagnostic work-up to determine both the presence and etiology of any suspected cognitive impairment. Additional benefits include the utility of a relatively brief cognitive screening tool that is non-invasive and can be administered by a non-clinician.

Additional factors to be considered in determining probable risks and benefits for Cognivue include: (1) the study was a blinded, multi-site controlled clinical trial and (2) there currently are no legally marketed computerized cognitive assessment aids for determining cognitive dysfunction.

In conclusion, the data support that for an computerized cognitive assessment aid for determining evidence of cognitive impairment which is intended to be used as an assessment aid that is part of a full medical work-up for cognitive impairment, the probable benefits outweigh the probable risks for Cognivue. The device should not be used as a stand-alone diagnostic device, and does not identify the presence or absence of clinical diagnoses. The device provides benefits and the risks can be mitigated by the use of general and special controls.

CONCLUSION

The *de novo* for Cognivue is granted and the device is classified under the following:

Product Code: PKQ
Device Type: Computerized Cognitive Assessment Aid
Class: Class II
Regulation: 21 CFR 882.1470