Evaluation of DCTclock as a Cognitive Assessment Aid

Protocol Identifying Number: DCT032

Draft or Version Number: 3

January 3, 2018

Study Product: DCTclock™

Study Sponsor: Digital Cognition Technologies, Inc.

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LIST OF ABBREVIATIONS

GCP	Good Clinical Practice
CFR	Code of Federal Regulations
IRB	Institutional Review Board
MMSE	Mini Mental State Exam
D-KEFs	Delis-Kaplan Executive Function System
WAIS	Wechsler Adult Intelligence Scale
AD	Alzheimer's Disease
PD	Parkinson's Disease
MoCA	Montreal Cognitive Assessment
AE	Adverse Event
FDA	Food and Drug Administration
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
CRF	Case Report Form
SOP	Standard Operating Procedures
DCT	Digital Cognition Technologies, Inc.
ICF	Informed Consent Form
SRM	Study Reference Manuals
DSMB	Data Safety Monitoring Board
SLUMS	St. Louis Mental Status
SAP	Statistical Analysis Plan
ITT	Intention To Treat
PPA	Positive Percent Agreement
NPA	Negative Percent Agreement
TEAE	Treatment Emergent Adverse Event
HIPAA	Health Insurance Portability and Accountability Act
MDR	Medical Device Reporting

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, ICH E6 and/or 21 CFR Part 812).

The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

_____ Print/Type Name

Signed:

_____ Signature

Date:_____

PROTOCOL SUMMARY

Title:

Evaluation of DCTclock as a Cognitive Assessment Aid

Précis:

This study uses a paired design in which each subject undergoes blinded testing by separate testers administering DCTclock and a battery of reference standard tests to determine cognitive state. Test-retest reliability of both DCTclock and the reference standard, Mini Mental State Exam (MMSE) will be conducted by comparing performance on the initial test to performance on a subsequent test following a one to four-week interval. 500 subjects will be recruited to participate with the anticipation that 400 will be available for analysis.

Objectives:

The overall objective of this study is to demonstrate the safety and effectiveness of DCTclock as an adjunctive tool for use by clinicians to evaluate cognitive function in adults aged 55-95. There are four specific aims of the proposed project.

Aim 1: Examine the agreement between DCTclock classifications and a reference standard, the MMSE.

Aim 2: Determine the test/re-test reliability of DCTclock

Aim 3: Determine the construct validity of DCTclock via comparison with traditional paper and pencil neuropsychological tests.

Aim 4: Characterize the safety profile for DCTclock

Endpoint

Primary endpoint: DCTclock and MMSE assessment of impaired, unimpaired or Indeterminate/intermediate status. The primary analysis will assess agreement of DCTclock with the reference standard, MMSE in identifying unimpaired and impaired test subjects.

Secondary endpoint: DCTclock scores, MMSE scores and assessment of DCTclock and MMSE impaired and unimpaired status at each of two time points. The secondary analysis will assess the comparability of DCTclock test-retest reliability to that of MMSE.

Additional endpoint: DCTclock scores, MMSE scores and neuropsychology battery scores. The goal of analysis on these endpoints is to assess construct validity of DCTclock. Specifically, the goal is to compare scores from the repeated administration of DCTclock to the repeated administration of a battery of neuropsychological tests, to characterize the psychometric properties of DCTclock and to compare those properties to the properties of MMSE.

Safety endpoint: Incidence of serious device-related adverse events

Population: Healthy adults aged 55-95

Phase:	Pivotal
Number of Sites enrolling participants:	2-4
Description of Study Agent:	DCTclock, a digitized version of the standard pen and paper neuropsychological clock drawing test, is a non-invasive, computer-based cognitive assay. The test involves participants drawing two clock faces on a piece of paper with a digital pen that precisely tracks and records drawing behavior. The positional data generated during this assessment is then analyzed by proprietary algorithms that evaluate hundreds of features captured in the pen stroke information. By comparing test results to normative data, the system then determines whether the test falls inside or outside normal limits and provides a detailed breakdown of performance on the various cognitive processes evaluated during the test.
Study Duration:	6 months
Participant Duration:	4 weeks

SCHEMATIC OF STUDY DESIGN

1. Subject recruitment.
2. Those subjects who meet the inclusion criteria will be consented (Administrator #1).
3. Screening tests and the DCTclock test will be administered (Administrator #1).
    a. Screen for impairment of dominant hand
    b. Screen for drug/alcohol use
    c. Reading and comprehension assessment
    d. Hamilton-Veale Contrast Sensitivity [1]
    e. DCTclock
    f. Purdue Peg Board [2]
4. The Neuropsychological test battery and questionnaire will be administered (Administrator #2).
    a. MMSEworld [3]
    b. MoCA [4]
    c. Benton Judgement of Line Orientation [5]*
    d. Rey Complex Figure [6]*
    e. Delis-Kaplan Executive Function System (D-KEFs) Verbal Fluency (sub-test of D-KEFs) [7]*

f. Digit Span and Reliable Digit Calculation (sub-test of Wechsler Adult Intelligence Scale-WAIS-IV) [8]

g. Block Designs (sub-test of WAIS-IV) [8]*

h. Trail Making Test – Parts A and B [9]

i. Symbol Digit Modalities [10]*

j. Geriatric Depression Scale (15 item version). [11]*

5. Repeat steps 3 and 4 (above) in the same subjects after one to four weeks without feedback, minimizing learning effects.

Assessments indicated with an asterisk (*) above will only be given to participants who complete visit 1 under protocol version 1.

1 KEY ROLES

Sponsor:

Digital Cognition Technologies

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Cognitive impairment, specifically Dementia and Alzheimer's Disease, is one of the largest health problems in the United States. There are 6 million individuals in the U.S. with some form of Dementia, representing an annual cost to the healthcare system of $225 billion. 5.3 million of these people have Alzheimer's Disease, the 6th leading cause of death in the U.S. By 2050, these numbers are expected to triple to nearly 16 million Americans diagnosed with dementia, with an annual cost of more than $1 trillion [12]. Current standard of care to address this enormous health problem are lengthy for both practitioners and patients, potentially invasive, expensive, and cannot detect impairment early enough to intervene and potentially change the course of disease. There is an enormous market need for a cost effective, reliable, objective, noninvasive, accurate, way to identify cognitive impairment at its earliest stages.

The Traditional Clock Drawing Test

The Clock Drawing Test has been a widely accepted cognitive screening tool for more than 50 years. The Clock Drawing Test is one of the top 40 most commonly used tests by neuropsychologists in the US and Canada [13] and is used internationally to assess for dementia and other neurological disorders [14]. The Clock Drawing Test is relatively straightforward and is easy to administer; the test asks the patient to draw on a blank sheet of paper a clock showing "10 minutes after 11" (the "Command" clock), then asks them to copy a pre-drawn clock showing that time (the "Copy" clock). The test measures constructional, spatial, and executive abilities, and deficits in the conception of time [15]. The Clock Drawing Test requires different cognitive capabilities in the two drawing conditions: the command clock relies more heavily on memory and language processing, while the copy clock relies more on executive function and visual-spatial perception.

The Clock Drawing Test is useful as a screening tool to differentiate normal elderly individuals from those with obvious cognitive impairment and has proven useful in helping to diagnose dementias, stroke, Alzheimer's Disease(AD), Parkinson's Disease (PD), and other conditions [16, 17, 18].

Limitations of The Traditional Version

The Clock Drawing Test is cleverly designed and easy to administer, but has several functional drawbacks. Due to the reliance on clinical judgment in scoring the finished clock drawing, there can be large variability in scoring. Attempts to formalize scoring have produced systems that are either too labor intensive and time consuming to be widely useful [19] or, if fast, are insufficiently reliable [18] or insufficiently accurate [20].

The traditional test (and its scoring systems) also rely only on the final product of the test, not considering the drawing process. Capturing the drawing process adds substantially to the utility of the clock drawing task as a cognitive assessment tool. Research indicates that cognitively healthy individuals spend about 60 percent of their time on the test thinking (i.e., holding the pen but not drawing), therefore, to date 60 percent of test data has not been analyzed. That research has also determined that there is diagnostic information in drawing processes (i.e., the percent of time spent thinking vs. "inking," i.e., writing on the page) [21].

Finally, the traditional test relies on the analysis of errors in the drawing product, essentially waiting for patients to fail before indicating a problem. Prior to overt impairment, people use compensatory strategies to address cognitive deficits associated with very early impairment. These strategies reduce errors in the final product, often leaving very mild impairment undetected.

DCTclock™

DCTclock™ is a neuropsychological test based on the traditional Clock Drawing Test that may provide a more sensitive measure of cognitive state. The DCTclock test, offered by Digital Cognition Technologies (DCT), capitalizes on the clever design of the traditional clock drawing test but uses patented advanced

analytics and technology to evaluate both the final drawing and the process that created it, producing a more robust assessment. DCTclock uses a digitizing ballpoint pen that, while drawing, also digitally records its position on the paper 75 times a second with a spatial resolution of two one-thousandths of an inch. DCT software detects and measures changes in pen position that cannot be seen by the naked eye, and because the data is time-stamped, the system captures the entire sequence of behaviors (e.g., every stroke, pause or hesitation), rather than just the final result. This enables the capture and analysis of very subtle behaviors that have been found to correlate with changes in cognitive function. These measurements are all operationally defined in DCT code (hence free of user bias) and carried out in real time.

DCTclock hardware includes the digitizing pen, pen dock, and printed test form. [redacted] As a participant draws, the pen captures and encrypts the test data. The data from the pen is securely transmitted to DCT's HIPAA compliant servers where it is decrypted, then analyzed using advanced analytics including proprietary state-of-the-art artificial intelligence and machine learning techniques. Over 700 individual features are analyzed for each DCTclock test. Of the 700 features, a few dozen have been found to correlate well with changes in cognitive function. Following test analysis, a report is instantly generated and immediately available for review by the investigator via a secure website. [redacted] This advanced technology is no more complex for an examiner or subject to use than an ordinary ballpoint pen, ensuring no barriers to widespread use.

[redacted]

2.2 RATIONALE

The goal of this study is a prospective validation of the DCTclock test as a reliable and accurate measurement of cognitive performance. Data collected will be used to establish the validity of DCTclock scoring and a comparison to the reference standard, the MMSE, as well as assessing test-retest reliability by testing participants twice over a four-week period.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

The digital clock drawing test has been used in research and clinical settings for over 10 years with no reported adverse events in the literature [21-24]. DCTclock differs from the digital clock drawing test predominantly in the automation of the analysis. Where the digital clock drawing test required user intervention to classify pen strokes, DCTclock has fully automated that process. It is reasonable to assume that the risk level for DCTclock will be similar for that seen with the digital clock drawing test.

- Cognitive testing can result in general fatigue but participants will be allowed breaks between tests, as necessary, to alleviate any fatigue.
- No results from the testing conducted in this protocol will be shared with participants or used to guide their clinical care. Should a participant express any concern with their performance, they will be directed to discuss those concerns with their Primary Care Physician.
- While there is always a risk of loss of confidentiality of study data, all data will be stored securely at the sites and de-identified prior to sharing with the sponsor.

Cognitive tests can only be validated through use on human subjects. As the risks associated with this study are minimal, the benefits of validation of a sensitive assessment of cognitive state outweighs the potential risks.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no direct benefit to study participants.

3 OBJECTIVES AND PURPOSE

The overall objective of this study is to demonstrate the safety and effectiveness of DCTclock as an adjunctive tool for use by clinicians to evaluate cognitive function in adults aged 55-95. There are four specific aims of the proposed project.

Aim 1: Examine the agreement between DCTclock classifications and a reference standard, the Mini-Mental State Exam (MMSE).

Aim 2: Determine the test/re-test reliability of DCTclock

Aim 3: Determine the construct validity of DCTclock via comparison with traditional paper and pencil neuropsychological tests.

Aim 4: Characterize the incidence of serious device related adverse events

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This study uses a paired design in which each subject undergoes blinded testing by separate examiners. One examiner assesses eligibility and administers the DCTclock test and the other examiner administers a battery of reference standard tests. DCTclock is the only investigational assessment. Test-retest reliability of both DCTclock and the reference standard, MMSE, will be conducted following a one to four-week interval after initial testing. 500 subjects will be recruited to participate in this pivotal trial to obtain 400 evaluable subjects. Subjects will undergo the same testing at two separate visits within 4 weeks.

4.1.1 PRIMARY ENDPOINT

Primary endpoint: DCTclock and MMSE assessment of impaired, unimpaired or indeterminant/intermediate status. The primary analysis will assess agreement of DCTclock with the reference standard, MMSE, in identifying unimpaired and impaired test subjects.

4.1.2 SECONDARY ENDPOINT

Secondary endpoint: DCTclock scores, MMSE scores and assessment of DCTclock and MMSE impaired and unimpaired status at each of two time points. The secondary analysis will assess the comparability of DCTclock test-retest reliability to that of MMSE.

4.1.3 ADDITIONAL ENDPOINT

Additional Endpoint: DCTclock scores, MMSE scores and neuropsychology battery scores. The goal of analysis on these endpoints is to assess construct validity of DCTclock. Specifically, the goal is to compare scores from the repeated administration of DCTclock to the repeated administration of a battery

of neuropsychological tests, to characterize the psychometric properties of DCTclock and to compare those properties to the properties of MMSE.

4.1.4 SAFETY ENDPOINT

Safety endpoint: Incidence of serious device related adverse events

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

- Men and women 55-95 years old.

5.2 PARTICIPANT EXCLUSION CRITERIA

- 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 Arial, 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:
  - "You are being asked to join a research study because you are 55-95 years old and you are interested in evaluating a new assessment of your mental processing. In order to decide if you should participate in this study, you should know enough about the risks and benefits. This process is known as informed consent."
- Inability to answer three questions about testing after consent is read to the subject:
  - How long does each session take? (Correct response is approximately 60 or 110 mins per session.)
  - How many sessions are there? (Correct response is a total of two sessions.)
  - How much will you be getting paid? (Correct response is fifty dollars per session.)
- Assessment of impairment of the writing hand that precludes ability to perform the DCTclock test. The participant will be asked whether they have suffered any significant injury or other physical change in function that would prevent them from holding a pen and writing. An answer of 'yes' would be an exclusion criteria.
- Impaired manual dexterity in the writing hand as judged by timed performance below cut-off standards (quantified by Purdue Peg Board score < 6).
- Impaired vision of both eyes as judged by poor contrast sensitivity (quantified by Hamilton-Veale Contrast Sensitivity < 7).
- Under the influence of recreational drugs or alcohol at the time of the visit.
- Current or recent (within the last 6 months) participation in a clinical trial that includes the use of a drug or intervention to alter cognitive function.
- Recent (within the last 6 months) cognitive testing with MoCA, MMSE, or another Clock Drawing Test.
- Visit 2 Only:
  - Any self-reported change (addition or discontinuation) of the following medications between visit 1 and visit 2; Timolol (eye drop), Benadryl, beta blockers, steroids or over the counter medications for sleep (PM varieties).

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited from several retirement communities and neurology practices. Recruitment materials will be used to find subjects. Participants will be compensated for their time at a rate of $50 per completed study visit (up to two visits).

The target evaluable sample size for analysis is 400. We intend to enroll in such a manner that 200 are from the general community (and hence are most likely cognitively unimpaired) and 200 from Neurology clinics (and hence more likely to be cognitively impaired). 500 participants will be screened. The anticipated accrual rate is 50 participants per site per month. Enrollment will be completed in 6 months.

One to two US sites will be used in this study. Participants will be recruited from the general population and referred from neurology clinics. The study will be advertised in these areas using local fliers and print ads in regional papers. Participants will also be approached for participation if they are participating in other research at the sites that does not include the use of a drug or intervention to alter cognitive function and if the participant has not received cognitive testing (including MoCA, MMSE, Clock Drawing Test) within 6 months.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participants who withdraw or terminate from the study will not be pursued as the study has no follow-up or long term safety and effectiveness endpoints. Participants who withdraw or do not complete the second visit will not be replaced as the overall sample size will take into account potential withdrawals.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigators and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

DCTclock™ is a neuropsychological test, based on the traditional clock drawing test, that uses a digital pen to capture clock images drawn by the participant and advanced analytics to evaluate the drawing process for indicators of cognitive change.

The DCTclock system is an investigational device consisting of both hardware and software. DCTclock hardware includes a digital pen and paper test form printed with a faint dot pattern. After docking the pen, a data transfer software program transmits the encrypted pen data to DCT's HIPAA compliant servers. Tests are decrypted there, then identified by the test administrator, analyzed using DCT's proprietary algorithm, and presented through the DCTreports™ portal (DCTclock software).

In the DCTclock test, participants are asked to spontaneously draw a clock picture and then copy a picture using a digitizing pen. De-identified, encrypted data is then sent to DCT for analysis and results are presented through the DCTreports web portal (see Figure 3).

[redacted]

[redacted]

The DCTclock test is non-invasive and does not introduce energy into the subject. Confidentiality loss is mitigated by robust data security processes. In this study, DCTclock results are not reported to participants or used to guide their clinical care.

Participants who take part in this study will receive standard paper and pencil neuropsychological testing in addition to the DCTclock test.

6.1.1 ACQUISITION

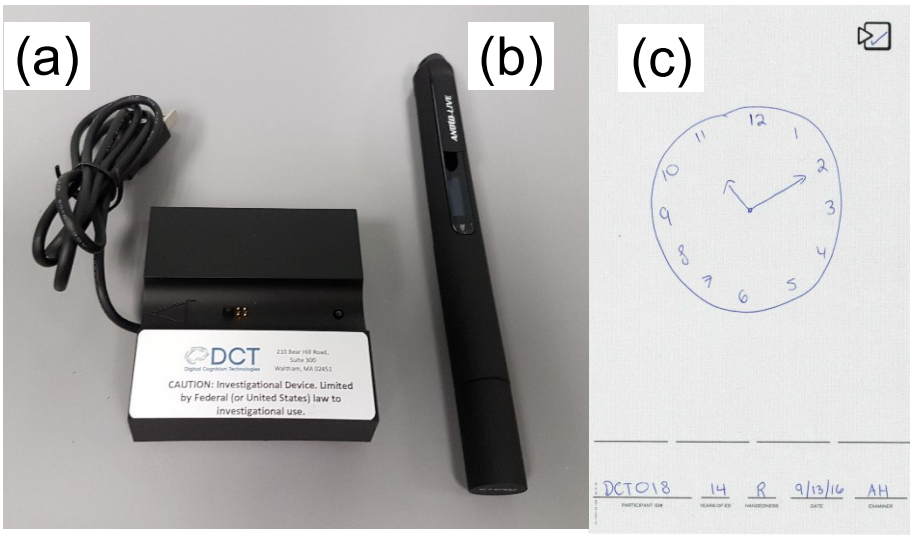
The study device, DCTclock, will be supplied to the sites by Digital Cognition Technologies, Inc. The commercially available neuropsychological tests will be purchased through standard channels.

6.1.2 APPEARANCE AND LABELING

The DCTclock system hardware consists of three main components (see Figure 4):

- [redacted] Dock (a) and Pen (b)
- DCTclock test form (c)

Figure 4: DCTclock Hardware



The DCTclock software consists of:

(a) DCTuploader- A locally installed software program to transmit pen data to DCT's servers for analysis
(b) DCTreports- A remotely hosted software platform that contains several sub-components
    - Data Ingestion: Pen stroke data are received and stored
    - Data Processing: Pen stroke data are processed and evaluated
    - Presentation: Test results are presented to administrator
    - Centralized administration tools: Remote devices and user accounts are managed

The device components will be labeled 'CAUTION: Investigational Device. Limited by Federal (or United States) law to investigational use.'

The product manual is contained within the DCTclock Investigator's Brochure.

6.1.3 PRODUCT STORAGE AND STABILITY

The DCTclock hardware should be stored in a secure location. As with any electronic device, it should not be exposed to water or extreme temperatures. The standard ambient conditions commonly found in medical office workspaces are acceptable.

6.1.4 PREPARATION

The DCTclock system will be installed by the sponsor and will be ready to use without additional preparation by the study site.

6.1.5 ADMINISTRATION

See the Investigator's Brochure for detailed DCTclock test administration instructions. Administration instructions for the standard neuropsychological tests are detailed in the Study Reference Manual (SRM).

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

DCTclock will be provided to the investigational site for use only in this study. The devices issued to each site will be logged. The site PI will be responsible for ensuring that the device is securely stored and used only accordance with the study protocol. DCTclock automatically logs the device information used to generate each test. The sponsor will ensure that all devices are collected and accounted for at the end of the study.

6.3 INDICATION FOR USE OF STUDY DEVICE

DCTclock is intended for use by clinicians as an adjunctive tool to evaluate cognitive function in adults aged 55-95. DCTclock, a digitized version of the standard pen and paper neuropsychological clock drawing test, is a non-invasive, computer-based cognitive assay.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

Prior to initiating the study at a site, the protocol and informed consent form (ICF) will be approved by the reviewing Institutional Review Board (IRB) for the site. SRMs will be provided to each site to access all related study materials.

Site personnel involved in the study will be trained on the following items prior to administering any aspect of the study:

- Protocol
- Administration of all assessment tools
- Use of the DCTclock system
- Data collection forms

7.1.1 STUDY SPECIFIC PROCEDURES

- Demographics and review of medical history and current medications
- Assessment of impairment of the dominant hand
- Assessment of recreational drug or alcohol use
- Reading and comprehension assessment
- Hamilton-Veale Contrast Sensitivity
- DCTclock
- Purdue Peg Board
- MMSEworld
- MoCA
- Benton Judgement of Line Orientation*
- Rey Complex Figure*
- D-KEFs Verbal Fluency (sub-test of D-KEFs)*
- Digit Span and Reliable Digit Calculation (sub-test of WAIS-IV)
- Block Designs (sub-test of WAIS-IV)*
- Trail Making Test – Parts A and B
- Symbol Digit Modalities*
- Geriatric Depression Scale (15 item version)*

  Assessments indicated with an asterisk (*) above will only be given to participants who complete visit 1 under protocol version 1.

  No results from these assessments will be provided to the participant.

7.2 LABORATORY PROCEDURES/EVALUATIONS

This study does not involve any laboratory procedures.

7.2.1 SPECIMEN PREPARATION, HANDLING, AND STORAGE

There are no specimens collected as part of this study.

7.3 STUDY SCHEDULE

7.3.1 SCREENING AND VISIT 1

Screening and Visit 1 (Day 1)

- Administrator #1 (consent, demographics + 14 min):
- Obtain informed consent of potential participant verified by signature on written informed consent form approved by the IRB. Eligible participants will be considered enrolled at the time of signing informed consent.
- Demographic information, medical history and current medication information collected.
- Screening tests and the DCTclock test will be administered in the following order:
  - Assessment of impairment of dominant hand- <1 min
  - Assessment of recreational drug and alcohol use- <1 min
  - Consent reading and comprehension assessment- 1 min
  - Hamilton-Veale Contrast Sensitivity test- 3 min
  - DCTclock test including demographics and recording of adverse device effects reported by participant or administrator- 3 min
  - Purdue Peg Board test- 5 min

- If a subject screen fails at any step, they will not complete the remaining assessments. Eligible subjects will then complete the study assessments.

- Administrator #2 (83 min for those who complete all assessments under version 1 of the protocol, 28 min for those who complete the bolded assessments below under version 2 of the protocol):
  - **MMSEworld- 10 min**
  - **MoCA- 8 min**
  - Benton Judgment of Line Orientation- 10 min
  - Rey Complex Figure- 15 min
  - D-KEFs Verbal Fluency Test- 10 min
  - **Digit Span and Reliable Digit Calculation - 5 min**
  - Block Designs- 10 min
  - **Trail Making Test A+B- 5 min**
  - Symbol Digit Modalities- 5 min
  - Geriatric Depression Scale (15 item version)- 5 min

7.3.2 VISIT 2 (FINAL STUDY VISIT)

Visit 2 (Day 8-29)

- Administrator #1 (14 min):
- Screening tests and the DCTclock test will be administered by Administrator # 1 in the following order:
  - Assessment of impairment of dominant hand- <1 min
  - Assessment of recreational drug and alcohol use- <1 min
  - Consent reading and comprehension assessment- 1 min
  - Hamilton-Veale Contrast Sensitivity test- 3 min
  - DCTclock test including demographics and recording of adverse device effects reported by participant or administrator- 3 min
  - Purdue Peg Board test- 5 min

If a subject screen fails at any step, they will not complete the remaining assessments. Eligible subjects will then complete the study assessments.

- Administrator #2 (83 min for those who complete all assessments under version 1 of the protocol, 28 min for those who complete the bolded assessments below under version 2 of the protocol):
  - **MMSEworld- 10 min**
  - **MoCA- 8 min**
  - Benton Judgment of Line Orientation- 10 min
  - Rey Complex Figure- 15 min
  - D-KEFs Verbal Fluency Test- 10 min
  - **Digit Span and Reliable Digit Calculation - 5 min**
  - Block Designs- 10 min
  - **Trail Making Test A+B- 5 min**
  - Symbol Digit Modalities- 5 min
  - Geriatric Depression Scale (15 item version)- 5 min

This visit ends the participant's participation in this study.

7.3.3 EARLY TERMINATION VISIT

This study will not include an early termination visit.

7.3.4 SCHEDULE OF EVENTS TABLE

Procedure	Screening/Visit 1	Visit 2	Administrator
Time	0	Within 1-4 weeks of visit 1	
Consent	X		1
Inclusion/Exclusion Criteria (Includes reading and comprehension assessments, dominant hand evaluation, and drug/alcohol use)	X	X	1
Hamilton-Veale Contrast Sensitivity	X	X	1
DCTclock Test and Demography	X	X	1
Assessment of adverse device effects	X	X	1
Purdue Peg Board	X	X	1
NP test battery:			

MMSEworld	X	X	2
MoCA	X	X	2
Benton Judgement of Line*	X	X	2
Rey Complex Figure*	X	X	2
D-KEFs Verbal Fluency*	X	X	2
Digit Span and Reliable Digit Calculation	X	X	2
Block Designs*	X	X	2
Trail Making Test	X	X	2
Symbol Digit Modalities*	X	X	2
Geriatric Depression Scale*	X	X	2

Assessments indicated with an asterisk (*) above will only be given to participants who complete visit 1 under protocol version 1.

7.4 CONCOMITANT MEDICATIONS

There are no medication restrictions for this study outside of those listed in the exclusion criteria. A current medication list will be collected at visit 1.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Although this study involves an investigational device, there is a low risk of any physical injury to participants. Any reports of unanticipated adverse device effects (UADEs) will be collected at each use of the device and reviewed centrally for reportability.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE is considered serious if in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing

hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects (21 CFR 812.3(s)).

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For all AEs the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 RELATIONSHIP TO STUDY AGENT

The clinician's assessment of an AE's relationship to the study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. All AEs will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.4 ADVERSE EVENT REPORTING PROCEDURES

All AEs will be monitored from study enrollment through completion of this study. All AEs will be recorded in the database. The Investigator is required to complete the adverse event CRF at each study visit, if an adverse event occurs. A description of the event, including the start date, resolution date, action taken and the outcome should be provided, along with the investigator's assessment of the relationship between the AE and the study treatment.

All AEs should be followed until the event is resolved or judged to be chronically stable. The Site will provide relevant follow-up information to the sponsor and/or their designated representative.

All SAEs must be reported to the sponsor and/or their designated representative, the respective IRB within 24 hours of the site becoming aware of the event. A completed SAE CRF must be submitted to the sponsor or designee within five (5) working days of the event. The minimum required data to be recorded for an SAE includes: date of event, type of event, duration of event, severity, action taken, outcome and, if appropriate, causality and possible relationship to the investigational device. The Investigator should report all serious adverse events to the reviewing IRB, as required.

To ensure participant safety, each UADE must be reported to the sponsor and the IRB/EC immediately, but not later than 10 working days of learning of its occurrence. The SAE CRF and any supporting documentation should then be immediately sent to the sponsor who will be responsible for notifying the FDA.

If there is a device malfunction or other observation, the Device Observation CRF requires the Investigator to notify the Sponsor immediately and indicate if the observation resulted in an adverse event and indicate if complications are related to the device, procedure or underlying disease.

In the event of a suspected observation or device problem, the device shall be returned to the Sponsor for analysis. Instructions for returning the investigational device are included in the Study Reference Manual.

8.5 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Medical Monitor with the appropriate expertise. The Medical Monitor will review AEs, SAEs and UADEs according to the AE/SAE Handling Plan. The Medical Monitor will provide its input to the study sponsor. Given the low risk nature of the product, there will be no formal data safety monitoring board (DSMB).

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- [redacted] or her designee will be the monitor for the sites in this study.
- On-site monitoring visits for data verification will occur only once at the end of the study.
- This monitoring visit will include 100% data verification.
- Monitoring reports will be distributed to the PI and study sponsor.
- Independent audits will not be conducted.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

The sponsor or their designee will monitor either on site or remotely, as applicable. Monitoring and auditing procedures developed by the sponsor or their designee will be followed. The investigator must make available all subject records and regulatory documentation at every monitoring visit. The monitor will evaluate the CRFs for completeness and clarity, and for verification of the data with any source documents. Any discrepancies found are to be clarified by the investigator or designee. Consideration for medical confidentiality and data protection will be maintained as best as possible at every visit.

10 STATISTICAL CONSIDERATIONS

The overall objective of this study is to demonstrate the safety and effectiveness of DCTclock as an adjunctive tool for use by clinicians to evaluate cognitive function in adults aged 55-95. From an effectiveness perspective, the study intends to prove that:

a. DCTclock is non-inferior to the reference standard, MMSE, in identifying unimpaired and impaired test subjects.
b. DCTclock shows test-retest reliability comparable to that of the MMSE.

The specific endpoints are as follows:

Primary endpoint: DCTclock and MMSE assessment of impaired, unimpaired or indeterminate/intermediate status. The primary analysis will assess agreement of DCTclock with the reference standard, MMSE, in identifying unimpaired and impaired test subjects.

Secondary endpoint: DCTclock scores, MMSE scores and assessment of DCTclock and MMSE impaired and unimpaired status at each of two time points. The secondary analysis will assess the DCTclock test-retest reliability and descriptively compare it to that of MMSE.

Additional endpoint: DCTclock scores, MMSE scores and neuropsychology battery scores. The goal of analysis on these endpoints is to assess construct validity of DCTclock. Specifically, the goal is to compare scores from the repeated administration of DCTclock to the repeated administration of a battery of neuropsychological tests, to characterize the psychometric properties of DCTclock and to compare those properties to the properties of MMSE.

Safety endpoint: incidence of device related adverse events.

10.1 STATISTICAL AND ANALYTICAL PLANS

There will be a formal statistical analysis plan (SAP) for this study outlining in detail the analyses to be provided for all variables collected during the study. The sections below summarize the analysis for the primary and secondary safety and effectiveness endpoints.

10.2 STATISTICAL HYPOTHESES

Participants will be categorized as impaired, not impaired or indeterminate/intermediate for each of DCTclock,MMSE, and MoCA using the first measurement obtained on each participant. A 3-by-3 table, with the rows being the DCTclock/MMSE cognitive status and with columns being the MoCA cognitive status, will be generated as follows.

		MoCA			
DCTclock/ MMSE		Impaired	Indeterminate/Intermediate	Unimpaired	Total
	Impaired	a	b	c	a+b+c
	Indeterminate/ Intermediate	d	e	f	d+e+f
	Unimpaired	g	h	i	g+h+i
	Total	a+d+g	b+e+h	c+f+i	a+b+c+d+e +f+g+h+i

10.3 ANALYSIS DATASETS

- Intention-to-Treat (ITT) Analysis Dataset: all enrolled participants
- Evaluable Analysis Dataset: all enrolled participants undergoing cognitive testing with both DCTclock and MMSE and who are not performing suboptimally (as determined by the Reliable Digit Score). This is the primary analysis set for effectiveness.
- Safety Analysis Dataset: all enrolled participants undergoing cognitive testing with DCTclock. This is the primary analysis set for safety.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

All subjects will undergo testing with DCTclock, MMSE, and MoCA. A non-inferiority analysis using a two-one-sided tests (TOST) approach will be conducted comparing the quadratic weighted kappa between DCTclock and MoCA to the quadaratic weighted kappa between MMSE and MoCA.

The remaining analysis comparing DCTclock to MMSE will be descriptive, providing two-sided 95% confidence intervals of important parameters when necessary.

Descriptive statistics include sample size, mean, standard deviation, median and quartiles for continuous variables, and counts and percents for categorical variables. All confidence intervals will be two-sided 95% confidence intervals, and all p-values will be two-sided, using a two-sided 0.05 level of significance. There will be no imputation of missing data. Statistical analysis will be conducted with R version 3.4 or higher.

10.4.2 ANALYSIS OF THE PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness analysis will be carried out using quadratic weighted kappa scores. A two-one-sided test (TOST) approach will be conducted, comparing the agreement between the MMSE and DCTclock scores with MoCA scores.

The kappa statistics will be calculated from the following table:

	MoCA

DCTclock/ MMSE		Impaired	Indeterminate/intermediate	Unimpaired	Total
	Impaired	a	b	c	a+b+c
	Indeterminate /intermediate	d	e	f	d+e+f
	Unimpaired	g	h	i	g+h+i
	Total	a+d+g	b+e+h	c+f+i	a+b+c+d+e+f+ g+h+i

This portion of the analysis will be carried out on the primary endpoint population and will only include scores from the first examination.

10.4.3 SAMPLE SIZE

Approximately 500 participants will be enrolled to obtain 400 evaluable participants. The evaluable sample size is the same as the evaluable sample size used in "De Novo Classification Request for Cognivue". The primary null and alternative hypotheses are:

$$H0: \kappa \leq 0.40 \quad \text{vs. } H1: \kappa > 0.40$$

where κ is the quadratic weighted kappa statistic calculated from the above DCT-MMSE classification table. Power for quadratic weighted kappa requires assumptions of the values on the diagonal and off-diagonal of the table, which is a large number of assumptions. Power will thus be calculated for the unweighted kappa which requires fewer assumptions. It is assumed that the quadratic weighted kappa will be similar to or larger in magnitude than the unweighted kappa and with similar standard error as the unweighted kappa, so the study will be powered to show that the unweighted kappa >0.4 with the expectation it will then be sufficiently powered to show that the quadratic weighted kappa >0.4. An evaluable sample size of 400 subjects yields at least 80% power to reject the above null hypothesis at one-sided 0.025 level of significance under the assumptions that: (1) the true kappa is 0.52 or more; (2) the marginal percentage of participants categorized as impaired is between 20% and 42.5% for DCTclock; (3) the marginal percentage of participants categorized as impaired for MMSE is the same as that for DCTclock; (4) the marginal percentage of participants categorized as unimpaired for DCTclock is the same as the marginal percentage of participants categorized as impaired for DCTclock; (5) the marginal percentage of participants categorized as unimpaired for MMSE is the same as that for DCTclock; and (6) the marginal percentage of participants categorized as indeterminate is between 15% and 60% for each of DCTclock and MMSE and is equivalent between DCTclock and MMSE.

10.4.4 SECONDARY AGREEMENT ANALYSIS

Agreement analysis: Additional agreement analyses between DCTclock and MMSE scores on detecting cognitive status will be carried out as follows:

- To better visualize the relationship between the two tests, the DCTclock and MMSE continuous scores will be plotted separately against the MoCA scores in a scatter plot, superimposed with a line of identity.
- Linear and rank linear regression analyses will be conducted and p-values with 95% CI will be calculated for the y-intercept and slope of each model. Either the Pearson (linear regression) or the Spearman (rank regression) correlation coefficients will be produced, and superimposed onto the scatter plots for each regression method, along with 95% confidence intervals and the estimated regression line.
- From Table I, the following statistics will be calculated for each of the tables (DCTclock vs MoCA and MMSE vs MoCA):

- Positive Percent Agreement (PPA) = a/(a+d+g)*100 and its 95% Wilson CI
- Negative Percent Agreement (NPA) = (e+f+h+i)/(b+c+e+f+h+i)*100 and its 95% Wilson CI.
- No formal hypotheses will be carried out on the PPA and NPA calculations, although 95% CIs will accompany them.

10.4.5 ANALYSIS OF SECONDARY EFFECTIVENESS ENDPOINTS

Participants will undergo cognitive testing with both the DCTclock and the reference standard, MMSE twice, where the second examination will be one to four weeks after the first examination. The secondary endpoints are DCTclock scores, MMSE scores and assessment of DCTclock and MMSE impaired and unimpaired status at each of two time points. The secondary analysis will assess the comparability of DCTclock test-retest reliability to that of MMSE. DCTclock test results of "unanalyzable" will be excluded from these analyses. Also, participants who no longer satisfy the inclusion/exclusion criteria prior to the second examination will also be excluded from this analysis.

Agreement analysis: For each of DCTclock and MMSE separately, the agreement between the first and second measurements will be carried out as follows:

1. A scatter plot of reading 2 vs. reading 1 will be generated, superimposed with a line of identity. An unweighted Deming regression (where the variance of the measurement error for each of DCTclock and MMSE is determined by the two measurements that were collected 1-4 weeks apart) will be carried out to determine the y-intercept, slope and their two-sided 95% confidence intervals. The correlation coefficient will also be determined. A hypothesis test of the slope vs. 1 and of the y-intercept vs. 0 will be carried out. Specifically, the following hypothesis test will be carried out:'
   H_0: $\beta_0 = 0$ vs. H_1: $\beta_0 \neq 0$ and H_0: $\beta_1 = 1$ vs. H_0: $\beta_1 \neq 1$

   where β_0 and β_1 are the y-intercept and slope, respectively, from the Deming unweighted regression.

2. Within each of DCTclock and MMSE separately, participants will be categorized as impaired, not impaired or indeterminate/intermediate for each of the two measurements obtained on each participant. A 3-by-3 table, with the rows being the second reading status and with columns being the first reading cognitive status, will be generated as follows for each of DCTclock and MMSE:

		Reading 1			
Reading 2		Impaired	Indeterminate/ Intermediate	Unimpaired	Total
	Impaired	a	b	c	a+b+c
	Indeterminate/ intermediate	d	e	f	d+e+f
	Unimpaired	g	h	i	g+h+i
	Total	a+d+g	b+e+h	c+f+i	a+b+c+d+e +f+g+h+i

   The following statistics will be calculated from the above table:

   Positive Percent Agreement (PPA): a/(a+d+g)*100 and its two-sided 95% Wilson confidence interval

   Negative Percent Agreement (NPA): (e+f+h+i)/(b+c+e+f+h+i)*100 and its two-sided 95% Wilson confidence interval.

A quadratic weighted kappa score will be generated along with its Wald two-sided 95% confidence interval. This analysis will be repeated with the indeterminate/intermediate groups omitted.

Percent agreement for impaired: a/(a+d+g)*100 and its two-sided 95% Wilson confidence interval.

Percent agreement for indeterminate/intermediate: e/(b+e+h)*100 and its two-sided 95% Wilson confidence interval.

Percent agreement for unimpaired: i/(c+f+i)*100 and its two-sided 95% Wilson confidence interval.

3. Within each of DCTclock and MMSE separately, participants will be categorized as impaired, not impaired or indeterminate/intermediate at each of the two measurements obtained on each participant. A 3-by-3 table, with the rows being the second reading status and with columns being the first reading cognitive status, will be generated as follows for each of DCTclock and MMSE:

		Reading 1			
Reading 2		Impaired	Indeterminate/ Intermediate	Unimpaired	Total
	Impaired	a	b	c	a+b+c
	Indeterminate/ Intermediate	d	e	f	d+e+f
	Unimpaired	g	h	i	g+h+i
	Total	a+d+g	b+e+h	c+f+i	a+b+c+d+ e+f+g+h+i

The Fisher-Freeman-Halton exact test will be used to assess if the cognitive classifications differ between reading 1 and 2 for each of DCTclock and MMSE. The null hypothesis is that reading 2 and reading 1 do not differ with respect to cognitive classifications.

4. If results show a significant difference between test and retest for DCTclock, that does not imply that DCTclock is less reliable than MMSE or other neuropsychological tests. The intraclass correlation for each of DCTclock test-retest difference, the MMSE test-retest difference, and neuropsychology battery variables' test-retest differences will be calculated. The test-retest weighted kappa statistic for determination of impaired status will also be calculated for DCTclock and MMSE. Results showing that DCTclock has similar or better ICC/ kappa than neuropsychological battery variables and MMSE will be considered as sufficient reliability of DCTclock.

10.4.6 OTHER EFFECTIVENESS ANALYSIS

Psychometric Validation (construct validity). The goal of this analysis is to compare scores from the repeated administration of DCTclock to scores from the repeated administration of a battery of neuropsychological tests, to characterize the psychometric properties of DCTclock and to compare those properties to those properties of MMSE. Pearson correlation coefficients will be used for bivariate assessments of the relationship of DCTclock scores to neuropsychological test scores and for MMSE scores to neuropsychological test scores.

Scatter plots of DCTclock and MMSE scores vs. the scores of separate neuropsychological battery tests will be presented with a Deming regression line superimposed on the scatterplot.

10.4.7 SAFETY ANALYSES

Safety analysis will be performed on the safety analysis set. Treatment emergent adverse events (TEAEs), which are events that started or worsened during or after the first DCTclock test, will be listed including start date of event and date of the DCTclock tests.

10.4.8 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics of baseline characteristics will be presented for the ITT and Evaluable populations and descriptively compared between the two populations. Also, to be inspected will be the baseline characteristics for the ITT participants not in the Evaluable population.

10.4.9 PLANNED INTERIM ANALYSES

There is no formal interim analysis for the study.

10.4.9.1 EFFECTIVENESS REVIEW

There will be no review of effectiveness at the interim.

10.4.9.2 SAFETY REVIEW

Testing with the study agent will be halted when three severe AEs determined to be “probably related” are reported to the sponsor. The study sponsor will notify investigators immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the FDA of the temporary halt and the disposition of the study. Given the low risk nature of the product, there will be no formal data safety monitoring board (DSMB) but there will be a safety Medical Monitor for the study.

10.4.10 SUB-GROUP ANALYSIS

All above effectiveness analyses (with the exception of the formal hypothesis test of the weighted kappa) may be repeated by (1) age (below median age, at or above median age); (2) sex; (3) education level; (4) language fluency test score (below median, at or above median) (5) medical history; and (6) current medications.

In addition, it is expected that the DCTclock test’s ability to identify impaired participants exceeds that of MMSE when participants are mildly impaired. Thus, for participants who score unimpaired on MMSE but impaired on DCTclock, scores on the neuropsychology battery test may be further inspected as follows to assess how often the DCTclock yielded the correct diagnosis in these cases. Specifically, the following will be presented on this subset of participants (when available):

- Percentage of participants scoring in the impaired range on the MoCA test (25 or below)
- Percentage of participants scoring 1.5 standard deviations below the mean on two or more of the following tests (Benton Judgement of Line, Rey Complex Figure, DKEFs, Digit Span, Blocks, Trails, Symbol Digit).
- Percentage of participants 2 standard deviations below the mean on one of the following tests (Benton Judgement of Line, Rey Complex Figure, DKEFs, Digit Span, Blocks, Trails, Symbol Digit).

10.4.11 MULTIPLE COMPARISON/MULTIPLICITY

Given the nature of the analysis, there will be no adjustment for multiple comparisons.

10.4.12 TABULATION OF INDIVIDUAL RESPONSE DATA

Individual participant scores will be listed for each of DCTclock and MMSE by time point for each participant. Demographic information and adverse events will also be listed for each participant.

10.5 MEASURES TO MINIMIZE BIAS

10.5.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

N/A

10.5.2 EVALUATION OF SUCCESS OF BLINDING

N/A

10.5.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

N/A

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with regulatory requirements and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

12 QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

This study will be performed in accordance with the relevant parts of the Code of Federal Regulations, ICH Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki and any other applicable regional and/or national regulations.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to any testing.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by the clinical site emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Information about subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Every reasonable effort will be made to protect the confidentiality of the subjects throughout the study.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or regulatory bodies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. In the event that a subject withdraws authorization to collect or use Personal Health Information, the investigator retains the ability to use all information collected prior to the withdrawal of

authorization. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Sponsor.

13.4.1 RESEARCH USE OF STORED DATA

Data collected under this protocol may be used by the sponsor for future research on cognition. Access to stored data will be limited to sponsor personnel. Data will be stored using codes assigned by the investigators. Data will be kept on password-protected computers.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is required to maintain detailed source documents on all subjects who are screened and/or enrolled in the study. Source documents include subject records, investigator subject trial files, as well as the results of tests and assessments. The date the subject began and exited the trial and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation should be included in the subject file.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Case Report Forms (CRFs) are used for the collection and recording of data at the Investigative Center. The investigator is responsible for the timely completion and updating of the CRF. Data reported in the CRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record.

Serious Adverse Events (SAEs) are to be reported within 24 hours of knowledge of the event.

Incoming data are reviewed to identify inconsistent or missing data and adverse events. Data issues will be addressed with the site and/or during site visits. All hard copy forms and data files will be secured to ensure confidentiality. Copies of the retrieved CRFs will be kept within the Trial Master File at the sponsor or the sponsor's designee.

14.2 STUDY RECORDS AND RETENTION

Study documents must be retained for a minimum of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records of no longer required to support FDA approval of the device or a notice of completion of a product development protocol. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

Investigator records shall include the following materials:

- **Correspondence:** Documentation of all verbal and written correspondence with FDA, the Sponsor, the Clinical Monitor and other investigators regarding this clinical study or any participant enrolled therein.
- **Subject records:** Signed informed consent forms, copies of all completed Case Report Forms and supporting documents (assessments, tests, etc.). Informed consent must comply with FDA regulations (21 CFR, part 50).
- **Investigational Plan (Clinical Study Protocol):** A current copy of the Clinical Study Protocol including Instructions for Use of the DCTclock device and blank case report forms.
- **Institutional Review Board (IRB) Information:** All information pertaining to IRB review and approval of this clinical study including a copy of the IRB letter approving the clinical study, a blank informed consent form approved by the IRB, and certification from the IRB Chairman that the IRB complies with FDA regulations (21CFR, Part 56)/regulatory body regulations, and that the IRB approved the clinical study protocol.
- **Investigator Agreements:** Copies of signed Investigator, Co-investigator and Sub-Investigator Agreements, as applicable, with accompanying curriculum vitae.
- **Other:** Any other records that may be required by applicable state or federal laws.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, or GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Prior approval from the sponsor is required for any deviation from the clinical study protocol except in the case of a deviation from the clinical study protocol intended to protect the life or physical well-being of a participant in an emergency. Prior approval from the reviewing IRB is also required if these changes or deviations are expected to affect the rights, safety or welfare of human subjects.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and reported to the sponsor or designee. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

The existence of this trial is confidential, and it should not be discussed with persons outside of the trial. Additionally, the information on this document and regarding this trial contains commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the trial who have need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied to the investigator that is indicated as confidential.

At the conclusion of the trial, a multi-center publication may be prepared for publication in a reputable scientific journal. Per the Publications Guidelines, any presentation/ publication of any data from this study must be approved by the sponsor prior to release. No independent publications by the individual sites will be allowed. Aggregated data may be published or presented in collaboration, with authorship determined by scientific convention.

15 INVESTIGATOR REPORTS

The Investigator will prepare and submit the following reports:

- MDR: Medical Device Reporting of all events related to the device or device malfunctions.
- Withdrawal of IRB Approval: Withdrawal of approval shall be reported to the sponsor or designee within five working days. The Investigator will provide a written report of the reason(s) approval was withdrawn.
- Progress Reports: The Investigator may be asked to submit progress reports to the reviewing IRB that include the number of study subjects, a summary of data and complications and a general description the study progress.
- Final Report: The investigator shall submit a final report within three months of termination or completion of the study or that investigator's participation in the study, to the IRB.
- Other Reports: Upon the request of FDA, the reviewing IRB, or the sponsor or designee, the investigator will provide accurate and timely information about any aspect of the clinical study.

16 TERMINATION OF STUDY OR STUDY SITE PARTICIPATION

The sponsor may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, the participating centers will be notified within five working days. All participants already enrolled will continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the final visit (or discharge) of the last enrolled participant.

The sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum participant enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

17 REGULATORY CONSIDERATIONS

Per 21 CFR 812.2(c)(3), diagnostic device studies are exempt as long as the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. This study meets the criteria for exemption from the general requirements of 21 CRF 812.

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VERSION INFORMATION

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