A Randomized Crossover Study to Assess the Reliability and Equivalence of Alternate Forms of the Digital Clock Drawing Test

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Study Product: DCTclock

Study Sponsor: Linus Health, Inc.

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LIST OF ABBREVIATIONS

GCP	Good Clinical Practice
CFR	Code of Federal Regulations
IRB	Institutional Review Board
DCTclock-pen	Original DCTclock test administered with a digitizing ball point pen and paper
DCTclock-tablet	A new version of the DCTclock test administered using a tablet and stylus
LAR	Legally Authorized Representative
MMSE	Mini-Mental State Exam
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
CDR-SOB	Clinical Dementia Rating Scale Sum of Boxes
AD	Alzheimer's Disease
PD	Parkinson's Disease
AE	Adverse Event
PI	Principal Investigator
FDA	Food and Drug Administration
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
CRF	Case Report Form
SOP	Standard Operating Procedures
ICF	Informed Consent Form
SRM	Study Reference Manuals
DSMB	Data Safety Monitoring Board
ITT	Intention To Treat
LoA	Limits of Agreement
ICC	Intraclass Correlation Coefficient
RMSD	Root Mean Squared Differences

MoCA	Montreal Cognitive Assessment
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:	**A Randomized, Crossover Study to Assess the Reliability and Equivalence of Alternate Forms of the Digital Clock Drawing Test**
Précis:	Randomized crossover trial consisting of two test visits separated by a washout period of 3 to 5 weeks. Subjects are randomized into two equal groups. Group 1 receives the digital pen (DCTclock-pen) version of the test at the first visit, with the tablet version (DCTclock-tablet) given at the second visit; Group 2 receives DCTclock-tablet at the first visit, followed by DCTclock-pen at the second visit. At Visit 1 (day 0), eligibility is assessed and a version of the DCTclock test is administered based on the group allocation. A battery of Linus Platform tests and reference standard tests are also administered. At visit 2 (day 21-35), eligibility is assessed and the alternate version of the DCTclock test is administered based on the group allocation. A battery of Linus Platform tests is also administered, together with reference standard tests. Equivalence of DCTclock-pen and DCTclock-tablet will be tested. Linus Platform test data will also be collected to develop novel measures of cognitive and motor function and assess their accuracy in detecting impairment, construct validity, and test-retest reliability. 200 subjects will be recruited to participate with the anticipation that 175 will be available for analysis.
Objectives:	The overall objectives of the study are to establish the equivalence of DCTclock-tablet to DCTclock-pen, to establish the safety of Linus Platform tests administered with a tablet or smartphone, and to collect data to enable the development and validation of Linus Platform tests. Aim 1: Validate equivalence between DCTclock-pen and DCTclock-tablet for subjects with diverse levels of cognitive impairment Aim 2: Characterize the safety profile of DCTclock-tablet and other Linus Platform tests Aim 3: Obtain data to develop and validate Linus Platform tests
Endpoint	Primary endpoint: - Equivalence of DCTclock-pen and DCTclock-tablet in assessing cognitive impairment. Exploratory endpoints: - Linus Platform tests individual and combined agreement with MMSE and RBANS assessment of cognitive status. - Test-retest reliability of both individual Linus Platform tests and the combined Linus overall score compared to the test-retest reliability of the RBANS. Safety endpoints: - Incidence of serious device-related adverse events.

Population:	Healthy adults aged 55-95
Phase:	Pivotal
Number of Sites enrolling participants:	1-3
Description of Study Agent:	DCTclock-tablet is an investigational device consisting of both hardware and software. Tablet hardware includes an Apple iPad and an Apple Pencil. An iPad application captures, encrypts, and transmits the encrypted data to Linus' secure servers. Tests are decrypted there, analyzed using a proprietary algorithm, and presented through a reporting portal in the same manner as the DCTclock-pen assessment. Linus Platform tests also consist of both hardware and software. Hardware includes either an Apple iPad and Apple Pencil or a smartphone. Linus Platform tests include additional drawing-based tasks, decision making and reaction time assessments, mood and lifestyle questionnaires, speech and voice analysis, eye-tracking based memory tests, and gait and balance measurements.
Study Duration:	9-12 months
Participant Duration:	Up to 5 weeks

SCHEMATIC OF STUDY DESIGN

1. Subject recruitment.

2. Those subjects who meet the inclusion criteria (men and women 55-95 years old) will be consented. Consent must be obtained from the subject or, if appropriate, their legally authorized representative (LAR) before any study procedures are completed.

3. Screening tests, a neurological assessment, one version of the DCTclock test, Linus Platform tests, and a standard neuropsychological test battery will be administered.

    a. Screen for impairment of the dominant hand

    b. Screen for drug/alcohol use

    c. Mini-Mental State Exam (MMSE) (1). The MMSE will not be administered if a documented MMSE or Montreal Cognitive Assessment (MoCA) score ≤18 exists in the subject records and an LAR has consented to the study.

    d. Hamilton-Veale Contrast Sensitivity (2)

    e. Purdue Peg Board (3)

    f. Brief neurological assessment

    g. DCTclock-pen or DCTclock-tablet

    h. Linus Platform drawing tasks with list learning

i. Linus Platform decision making and reaction time tests (4)

j. Linus Platform gait and balance assessment (5)

k. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (6)

4. After three to five weeks, screening tests, the alternate version of DCTclock, Linus Platform tests, and a standard neuropsychological test battery will be administered.

   a. Screen for impairment of dominant hand

   b. Screen for drug/alcohol use

   c. Alternate version of DCTclock from visit 1 (if DCTclock-tablet version was administered, then DCTclock-pen version is to be administered and vice versa)

   d. Linus Platform drawing tasks with list learning

   e. Linus Platform decision making and reaction time tests with PHQ-9 mood assessment

   f. Linus Platform lifestyle questionnaire (7)

   g. Linus Platform speech elicitation tasks (8)

   h. Linus Platform eye tracking-based memory assessments (9)

   i. Linus Platform gait and balance assessments

   j. RBANS

   k. Linus Platform reaction time test

1 KEY ROLES

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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 (10) . Current standard of care to address this enormous health problem is 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.

DCTclock™

DCTclock™ is a neuropsychological test based on the traditional Clock Drawing Test that may provide a more sensitive measure of cognitive state (11). The DCTclock test, offered by Linus Health, 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. The DCTclock test, is cleared to market and 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. DCTclock 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 code (hence free of user bias) and carried out in real time. To distinguish this version of the product, it will be referred to as DCTclock-pen. DCTclock-pen hardware includes the digitizing pen, pen dock, and printed test form. As a participant draws, the pen captures and encrypts the test data.

While DCTclock-pen is an easy-to-use and accurate cognitive test, enabling its administration using a tablet (DCTclock-tablet) will ease deployment by leveraging equipment more commonly found in clinical settings and that require less maintenance, with a concomitant decrease of cost and administrator burden. Hardware for DCTclock-tablet includes an Apple iPad and an Apple Pencil. Like the digital pen, the iPad captures and encrypts data as the participant draws with the Apple Pencil. In both cases – pen and tablet - the data from the DCTclock test is securely transmitted to Linus'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. Following test analysis, a report is instantly generated and immediately available for review by the investigator via a secure website. In addition to facilitating deployment by eliminating the need for unique hardware (the digitizing ballpoint pen), transitioning DCTclock to a tablet can also enable harmonization with other tablet-based cognitive assessment platforms such as the NIH Toolbox and tests under development in the Linus Platform.

The primary endpoint of this study is to determine the equivalence of DCTclock-pen and DCTclock-tablet in assessing cognitive impairment.

Linus Platform Tests

'Linus' is a multimodal, remote brain health monitoring platform designed to integrate scientifically validated, best-in-class technologies into a single 'plug-and-play' solution for longitudinal, in situ data collection. The platform brings together, into one mobile application, end-point solutions that rely mainly on smartphone or tablet sensors to collect various measures of patients' cognitive and motor functions. Linus Platform Tests will be included in this study to gather preliminary data. Ultimately, a battery of tests including DCTclock and others in the Linus Platform could be used clinically for a more accurate assessment of cognitive function, but it is first essential to determine how these tests correlate and complement each other by administering them in parallel in a defined cohort. An additional aim of this protocol is to obtain data to develop and validate tests on the Linus Platform. Linus Platform tests are at various stages of development and validation and include:

- Drawing-based tasks
- Measures of decision making and reaction time (4)
- Speech elicitation tasks (8)
- Eye tracking-based memory assessments (9)
- Gait and balance assessments (5)
- Lifestyle questionnaire

2.2 Rationale

The overall objectives of the study are to establish the equivalence of DCTclock-tablet to DCTclock-pen, to establish the safety of DCTclock-tablet and Linus Platform tests administered with a tablet or smartphone, and to collect data to enable the development and validation of Linus Platform tests.

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

DCTclock

DCTclock-pen is a class II, 510(k) exempt medical device and has been used in research and clinical settings with no reported adverse events. DCTclock's validation study (11) had the following safety outcome:

> 435 participants took a total of 841 DCTclock tests during the DCT032 study. A total of 37 adverse events (AE) were recorded in this population. The percentage of participants experiencing an AE during the study window (1-4 weeks) is not unexpected given that the study included an older population aged 55 to 95 years old. Of the total 37 AEs, only 1 was a serious adverse event (SAE). The SAE was reviewed by the study medical monitor and found to be unrelated to the protocol or study device. There were no reported unanticipated adverse device effects and no reported serious device related AEs.
>
> The 36 non-serious AEs were reviewed by the study Adverse Event Review Team and found to be unrelated to the study device. The most frequent AEs reported were colds and gastrointestinal upset and both occurred in less than 1 percent of participants (4 in 435).

DCTclock-tablet differs from DCTclock-pen predominantly in the use of an Apple iPad and Apple Pencil instead of the digitizing ballpoint pen and paper. It is reasonable to assume that the risk level for DCTclock-tablet will be minimal and the risk profile will be similar to that seen with DCTclock-pen.

Linus Platform Tests

- Additional drawing-based tasks where subjects draw on an iPad with an Apple pencil. Risks associated with this task are minimal and include fatigue and loss of confidentiality.
- A measure of decision making & reaction time where subjects tap the screen of a tablet in response to visual prompts. Risks associated with this task are minimal and include fatigue and loss of confidentiality.
- A speech elicitation task where subjects provide audio feedback such as describing a picture, recalling a story, reading sentences, and recalling lists of words using a tablet. Risks associated with this task are minimal and include fatigue and loss of confidentiality. This assessment includes voice recordings, but the recordings will not be associated with subject identifiers. This assessment requires subjects to remove any facial coverings for the duration of the task (~10 minutes).
- An eye tracking based memory assessment where subjects view images on a tablet screen. Images are later shown again with minor modifications and a video recording is used to determine the length of time the subject looks at each area of the screen. Risks associated with this task are minimal and include fatigue and loss of confidentiality. This assessment includes full face video recordings, but the recordings with not be associated with subject identifiers. This assessment requires subjects to remove any facial coverings for the duration of the task (~5 minutes).
- A gait and balance assessment where subjects complete short walking and standing tasks either with or without additional cognitive load (serial subtraction) while carrying a smartphone. The physical requirements are limited to standing with eyes open or closed for 30 seconds at a time (up to 2 min total) and walking at a comfortable pace for less than 2 minutes total. Although unlikely, the potential risks of these physical tasks include fatigue, sprains, muscle soreness and falling.
- A Lifestyle questionnaire where the subject responds to yes or no questions about their lifestyle on a tablet. Risks associated with this task are minimal and include fatigue and loss of confidentiality.

Overall Study Risks

- Cognitive testing can result in general fatigue, but participants will be allowed breaks between tests, as necessary, to alleviate any fatigue.
- Some minimal physical tasks are required for this study. Should a participant become uncomfortable completing the standing and walking tasks due to physical challenges or fatigue, they will be instructed to stop the task immediately.
- Should a participant express any concern with their performance on cognitive tests, they will be directed to discuss those concerns with their Primary Care Physician. No results from the testing conducted in this protocol will be shared with participants or used to guide their clinical care.
- Federal and local guidelines as well as site specific policies will be followed to minimize exposure of research subjects to COVID-19 in line with current clinical care.
- 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 transfer to the sponsor or their partners.

Cognitive tests can only be validated through use on human subjects. As the risks associated with this study are minimal, the benefit of validation of sensitive assessments 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 objectives of the study are to establish the equivalence of DCTclock-tablet to DCTclock-pen, to establish the safety of DCTclock-tablet and Linus Platform tests administered with a tablet or smartphone, and to collect the data to enable the development and validation of Linus Platform tests.

Aim 1: Validate equivalence between DCTclock-pen and DCTclock-tablet for subjects with diverse levels of cognitive impairment

Aim 2: Characterize the safety profile of DCTclock-tablet and the Linus Platform tests

Aim 3: Obtain data to develop and validate Linus Platform tests

4 STUDY DESIGN AND ENDPOINTS

4.1 Description of the Study Design

This study is a randomized crossover trial consisting of two test visits separated by a washout period of 3 to 5 weeks. Subjects are randomized into two equal groups. Group 1 receives DCTclock-pen at the first visit, with the DCTclock-tablet given at the second visit; Group 2 receives DCTclock-tablet at the first visit, followed by DCTclock-pen at the second visit. At Visit 1 (day 0), eligibility is assessed and a version of the DCTclock test is administered based on the group allocation. A battery of Linus Platform tests and reference standard tests are also administered. At visit 2 (day 21-35), eligibility is assessed and the alternate version of the DCTclock test is administered based on the group allocation. A battery of Linus Platform tests is also administered, together with reference standard tests. Equivalence of DCTclock-pen and DCTclock-tablet will be tested. Linus Platform test data will be collected to develop novel measures of cognitive and motor function and assess their accuracy in detecting impairment, construct validity, and test-retest reliability. 200 subjects will be recruited to participate with the anticipation that 175 will be available for analysis.

4.1.1 Primary Endpoint

Primary endpoint:

- Equivalence of DCTclock-pen and DCTclock-tablet in assessing cognitive impairment.

4.1.3 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 an inability to answer three questions about study details unless a LAR is available for consent.
    - How long do the sessions last (correct response is 1.5 to 2 hours- either individual answer is also acceptable)
    - How many sessions are there (correct response is 2)
    - How much will you be getting paid (correct response will vary by site)
- Impairment of the writing hand that precludes ability to perform the study tasks. 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 in 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 a Clock Drawing Test.
- Documented history of an MMSE or MoCA score of 18 or less or a score of 18 or less on the MMSE administered during screening unless a LAR is available for consent.
- 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

The target evaluable sample size for analysis is 175. 200 participants will be screened. The anticipated accrual rate is 22 participants per month. Enrollment will be completed in ~9 months.

One to three US sites will be used in this study with competitive enrollment. Participants will be recruited from the general population and referred from neurology clinics in order to recruit subjects with a range of cognitive function. 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 a Clock Drawing Test within 6 months.

Participants will be compensated for their time at a rate of $150 for two completed study visits. Subjects will receive $60 for the first completed study visit and $90 for the second completed study visit. Transportation costs will also be covered up to $75 per study visit at the site's discretion. Maximum total payment is $300 per subject for two completed visits. Payments will be made to the subject at the end of each visit. The study stipend may be prorated if the subject chooses not to complete all tasks on a given study visit.

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 Principal Investigator (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, or 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

DCTclock-pen is Class II, 510(k) exempt medical device (12).

DCTclock-tablet is an investigational device consisting of both hardware and software. Tablet hardware includes an Apple iPad and an Apple Pencil. An iPad application captures, encrypts, and transmits the encrypted data to Linus' HIPAA compliant servers. Tests are decrypted there, analyzed using a proprietary algorithm, and presented through a reporting portal.

In DCTclock-tablet, participants are asked to draw a clock picture according to audio instructions and then copy a picture of a clock using the study supplied Apple Pencil on an iPad.

Linus Platform Tests

Linus Platform tests include both FDA cleared and investigational devices consisting of both hardware and software. Hardware includes either a study supplied Apple iPad (with or without an Apple Pencil) or a study supplied smartphone.

Linus Platform drawing tasks

Linus is developing a series of drawing-based tablet tests administered with the Apple iPad and Apple Pencil. Just like with DCTclock, an analysis of drawing behavior will be conducted to identify early indications of cognitive change. An iPad application captures, encrypts, and transmits the encrypted data to Linus' HIPAA compliant servers. These drawing-based tasks include:

- Pre-test: An exercise involving copying waves that is administered before completing the other tablet tests (including DCTclock-tablet) with the only goal of making the subject comfortable with drawing using the Apple Pencil and the iPad.
- Pathfinding test: A series of mazes to be completed as quickly and accurately as possible.
- Symbol test: Keys of symbol-digit pairs are provided followed by prompts with empty boxes where the subject is asked to input the appropriate response as quickly as possible.
- Connect test: The subject is instructed to connect a set of circles as quickly as possible according to a pre-established pattern.
- Tracing test: The subject is asked to trace a line with both their dominant and non-dominant hand.

Linus Platform decision making and reaction time tests (4)

Participants will be asked to complete three short cognitive tasks presented on a tablet supplied by the study. These tasks are sourced from DANA Brain Vital (Anthrotronix, Inc.), which is an FDA-cleared, modular application that measures cognitive efficiency by tracking subtle changes in cognitive capabilities. DANA assessments are highly sensitive and designed for high-frequency use and focus on accuracy and reaction time—two key elements of cognitive efficiency. Each task takes 1-2 minutes to complete. Subjects will also be asked to complete the PHQ-9 depression screening tool (13). An iPad application captures, encrypts, and transmits the encrypted data to Linus' HIPAA compliant servers.

The tasks included are as follows:

Task	Description
Simple Reaction Time	A bullseye stimulus appears on the screen, and the test taker taps it as quickly as possible
Procedural Reaction Time	A number (1, 2, 3 or 4) appears on the screen, and the test taker must indicate which number was displayed by tapping either the "1 or 2" button or the "3 or 4" button
Go/No-go	A building with six windows is displayed, and either a "friend" (green) or "foe" (gray) alien will appear in a window. The test taker must tap the "BLAST" button only when foe stimuli appear
PHQ-9	Self-reported depression screening tool

Linus Platform speech elicitation tasks (8)

Linus utilizes a clinical-grade speech elicitation and analytics system designed to extract outcome measures as indicators of neurological system function from research participants. Tests will be administered, and voice recordings captured and encrypted on a study provided tablet. Voice recordings are then uploaded to a secure, HIPAA compliant cloud server managed by the test manufacturer, Aural Analytics, Inc. Transcripts of the voice recordings are created, and an AI engine analyzes for finite but clinically relevant information. Algorithms apply signal processing and cognitive linguistic analysis to assess speech and fine motor skills and detect subtle changes in cognitive function. Extraction of linguistic and phonetic measures have been previously shown to correlate to Alzheimer's disease and cognitive function. Speech and voice assessments may include:

Task	Description
Complex Picture Description	Participants describe a picture of a complex scene in their own words

Category Naming	Participants name as many items as they can that belong to a category
Object Recall	Participants name a set of objects after a short delay
Sentence Reading	Participants read a set of experimentally-controlled sentences
Sustained Phonation	Participants hold out a sustained vowel sound (/a/) for as long as possible
Diadochokinetic Rate	Participants repeat a set of alternating sounds (/bVtVkV/) as quickly as possible
Story Recall	Participants recall a short story both immediately and after a delay
List Learning	3-5 words are announced, and the subject is asked to recall those words both immediately after a short delay

Linus Platform eye tracking-based memory assessments (9)

VisMET (Visuospatial Memory Eye-Tracking Task) is a tablet-based application, developed by Emory University, that passively assesses visuospatial memory by tracking eye movements rather than memory judgements. VisMET offers a sensitive, and efficient memory paradigm capable of detecting objective memory impairment and predicting cognitive and disease status.

This task is conducted on an iPad and monitors a participant's gaze location and gaze patterns as they view repeated images that have been subtly changed between the first and second viewing of the image (for example, an item in the first image may have been deleted in the repeated image). This testing captures full face video recordings which will be kept and de-identified locally at the trial site. De-identified, coordinate level data will then be uploaded and a computerized algorithm will generate gaze position to approximate eye position. No other feedback from the participant is recorded. Cumulative gaze times, dwell times and other eye movement parameters serve as the study measures.

Linus Platform gait and balance assessment

Cognitive decline and neurodegenerative diseases have been implicated in gait dysfunction via disturbance of top-down mechanisms and frontal-systems' resource allocation and linked to executive dysfunction (14). Gait velocity decreases, variability increases, and the ability to multitask while walking (dual-tasking) is impaired as cognition declines and can be risk indicators of dementia progression (15). These features can be captured using motion sensors, such as accelerometers and gyroscopes on smart devices, and such approaches have been validated against in-lab measures (5). Dual tasking (e.g., walking or standing while performing a cognitive task) disrupts performance in one or both tasks, and resulting dual-task costs have been shown to increase with aging and be reliable indicators of loss of cognitive reserve and development of cognitive dysfunction and early dementia (16) (17). Specifically, dual tasking activates a network of brain regions, including prefrontal cortex, and is associated with degeneration of the entorhinal cortex (18). It offers a sensitive quantitative metric of integrity of frontal systems that correlate with executive function and serve as early biomarkers of meso-temporal memory systems.

This task is conducted using a study provided smartphone carried in a pocket or phone carrier attached to the subject's waist. In the gait assessment, the subject will be asked to walk at a comfortable pace of their choosing for 45 seconds. They will then be asked to repeat that walking exercise while performing a serial subtraction task. The total time walking is < 2 minutes. In the balance assessment, the subject is asked to

stand as still as possible for 30 seconds with their eyes open. They will then be asked to stand for 30 seconds with their eyes closed, and finally, to stand for 30 seconds with their eyes open while performing a serial subtraction task. Total standing time is < 2 minutes. Data from these tasks includes gyroscope and accelerometer readings.

Linus Platform lifestyle questionnaire

Adapted from the Barcelona Brain Health Initiative (7), this questionnaire includes up to 57 yes/no questions about the participant's lifestyle that are associated with cognitive performance. These questions are presented on a tablet and the subject uses their finger to select yes or no for each question.

Participants who take part in this study will also receive standard, accepted neuropsychological tests including RBANS (6) and MMSE (1) in addition to DCTclock and the Linus Platform tests.

All tests administered in this study are non-invasive and do not introduce energy into the subject. Study test results are not reported to participants or used to guide their clinical care. Additional information about the DCTclock-tablet and Linus Platform tests can be found in the Investigator's Brochure.

6.1.1 Acquisition

DCTclock-pen, DCTclock-tablet, and Linus Platform test tablet and smartphone hardware will be supplied to the sites by Linus Health, Inc. The commercially available neuropsychological tests will be purchased through standard channels.

6.1.2 Appearance and Labeling

Hardware

The DCTclock-tablet system hardware consists of two main components, an Apple iPad (Figure 1a) and an Apple Pencil (Figure 1b). Linus Platform tests will use the same hardware as DCTclock-tablet and also include a smartphone (Figure 1c).

Figure 1: Study Hardware

Software

As part of the Linus Platform, DCTclock-tablet system software consists of a locally installed iPad application to capture, encrypt, and transmit test data. The Linus Platform is a remotely hosted software platform that contains several sub-components

- Data Ingestion: Data are received and stored
- Data Processing: Data are processed and evaluated
- Presentation: Test results are presented to administrator
- Centralized administration tools: Remote devices and user accounts are managed

See DCTclock-tablet and Linus Platform Investigator's Brochure for images of Linus Platform test screens, subject instructions etc.

Labeling

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

6.1.3 Product Storage and Stability

All hardware should be stored in a secure location. As with any electronic device, the tablets, smartphones, and digital pens should not be exposed to water or extreme temperatures. The standard ambient conditions commonly found in office workspaces are acceptable.

6.1.4 Preparation

All hardware and software installation will be overseen by the sponsor or their representative 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 and Linus Platform test administration instructions. Administration instructions for the standard neuropsychological tests and DCTclock-pen are detailed in the DCTclock Manual and Study Reference Manual (SRM).

6.2 Study Agent Accountability Procedures

DCTclock-pen, DCTclock-tablet, and the Linus Platform test hardware 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 devices are securely stored and used only accordance with the study protocol. 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-tablet is intended for use by clinicians as an adjunctive tool to evaluate cognitive function in adults aged 55-95.

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
- Consent Form
- Investigator's Brochure
- Study Reference Manual
- Administration of all assessment tools including DCTclock and the Linus Platform tests.
- 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
- MMSE
- Hamilton-Veale Contrast Sensitivity
- Purdue Peg Board
- Brief neurological assessment
- DCTclock-pen
- DCTclock-tablet
- Linus Platform tests
    - Drawing-based tasks
    - Decision making & reaction time tasks
    - Mood assessment (PHQ-9)
    - Lifestyle questionnaire
    - Speech elicitation tasks

- Eye tracking-based memory assessments
- Gait and balance assessments

- RBANS

No results from these assessments will be provided to the participant or used to guide their clinical care.

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

Visit 1 (Day 1) ~120 minutes total

Visit 1 Screening (40 mins)	Time Estimate
Obtain informed consent of potential participant verified by signature on written informed consent form approved by the IRB. Consent must be obtained before any study assessments are completed.	15 mins
Demographics and review of medical history and current medications	5 mins
Assessment of impairment of the dominant hand	1 min
Assessment of recreational drug or alcohol use	1 min
MMSE	10 min
Hamilton-Veale Contrast Sensitivity	3 mins
Purdue Peg Board	5 mins

If a subject screen fails at any step, they will not complete the remaining assessments; eligible subjects complete the following study assessments.

Visit 1 Study Assessments (81 mins)	Time Estimate
Brief neurological assessment	20 min
Randomized to receive DCTclock-pen or DCTclock-tablet	1 min
DCTclock-pen or DCTclock-tablet	5 mins
Linus Platform drawing tests with list learning	15 mins
Linus Platform decision making and reaction time assessments	5 mins
Linus Platform gait and balance assessments	5 mins
RBANS	30 mins

7.3.2 Visit 2 (Final Study Visit)

Visit 2 (Day 21-35) ~ 94 minutes total

Visit 2 Screening (2 mins)	Time Estimate
Assessment of impairment of the dominant hand	1 min

Assessment of recreational drug or alcohol use/change in medications	1 min

If a subject screen fails at any step, they will not complete the remaining assessments; eligible subjects will complete the following study assessments.

Visit 2 Study Assessments (92 mins)	**Time Estimate**
Alternate version of DCTclock from visit 1 (if DCTclock-pen version was administered, then DCTclock-tablet version is to be administered and vice versa based on randomization group allocation)	5 mins
Linus Platform drawing tests with list learning	15 mins
Linus Platform decision making and reaction time assessments with PHQ-9	10 min
Linus Platform lifestyle questionnaire	10 min
Linus Platform speech elicitation tasks	10 min
Linus Platform eye tracking-based memory assessment	5 mins
Linus Platform gait and balance assessment	5 mins
RBANS	30 min
Linus Platform reaction time assessment	2 mins

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

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7.3.4 Schedule of Events Table

Procedure	Screening/Visit 1	Visit 2
Time	Day 0	Within 3-5 weeks of visit 1
Consent	X	
Inclusion/Exclusion Criteria	X	X
Medical History/Demographics	X	
MMSE	X*	
Hamilton-Veale Contrast Sensitivity	X	
Purdue Peg Board	X	
Brief Neurological Assessment	X	
DCTclock Test (either digital pen or tablet version)	X	X
Linus Platform drawing tests	X	X
Linus Platform decision making and reaction time assessments	X	X^ &
Linus Platform lifestyle questionnaire		X
Linus Platform gait and balance assessment	X	X
RBANS	X	X
Linus Platform speech elicitation assessments	X#	X
Linus Platform eye tracking-based memory assessments		X
Assessment of adverse device effects	X	X

*- MMSE not administered if a LAR consents to the study due to a documented prior MMSE or MoCA score of ≤18

& PHQ-9 depression screen is included in the decision making and reaction time assessments on visit 2 only

^ reaction time only is assessed twice on visit 2

#- List learning only is combined with the drawing tests on visit 1. All speech and voice assessments are given on visit 2.

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 investigational devices, 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, recorded individually (per test) 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 for each test. 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).

- A monitor will be assigned for the sites in this study.
- On-site monitoring visits for data verification will occur.
- 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 objectives of the study are to establish the equivalence of DCTclock-tablet to DCTclock-pen, to establish the safety of DCTclock-tablet and other Linus Platform tests administered with a tablet or smartphone, and to collect data to enable the development and validation of Linus Platform tests.

The specific endpoints are as follows:

Primary endpoint:

- Equivalence of DCTclock-pen and DCTclock-tablet in assessing cognitive impairment.

Exploratory endpoints:

- Linus Platform tests individual and combined agreement with MMSE and RBANS assessment of cognitive status. Study data will be split into training and testing subsets, with the training subset used to create a Linus overall score based on the individual Linus Platform tests and the testing subset used to validate the Linus overall score and each individual Linus test score by assessing their agreement with MMSE and RBANS.
- Test-retest reliability of both individual Linus Platform tests and the combined Linus overall score compared to the test-retest reliability of the RBANS.

Safety endpoints:

- Incidence of serious device-related adverse events.
    - o DCTclock tablet
    - o Linus Platform tests

10.1 Statistical and Analytical Plans

There will be a formal statistical analysis plan 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 additional safety and effectiveness endpoints.

10.2 Analysis Datasets

- Intention-to-Treat (ITT) Analysis Dataset: all enrolled participants.
- Evaluable analysis dataset: all enrolled participants undergoing cognitive testing with both DCTclock-pen and DCTclock-tablet and the Linus Platform tests.
- Validation dataset: A randomly selected subset of 50 subjects from the Evaluable Analysis Dataset. This is the primary analysis set for effectiveness.
- Training dataset: Subjects from the Evaluable Analysis Dataset that were not selected for the validation dataset.
- DCTclock and Linus Platform safety analysis dataset: all enrolled participants undergoing cognitive testing with DCTclock (DCTclock-pen and/or DCTclock-tablet) and the Linus Platform tests. This is the primary analysis set for safety.

10.3 Description of Statistical Methods

10.3.1 General Approach

All subjects will undergo testing with DCTclock-tablet, DCTclock-pen, Linus Platform tests, and RBANS. The DCTclock analysis algorithm generates an overall score (DCTclock score) of performance on the test, as well as a set of Composite Scales: Drawing Efficiency, Information Processing, Simple and Complex Motor, and Spatial Reasoning. The training dataset will be used to both adjust the DCTclock analysis algorithm and create Linus Platform algorithms. The validation dataset will be used to validate the DCTclock equivalence and Linus Platform test endpoints. Descriptive statistics will be measured on both the overall score and the composite scales. There will be no imputation of missing data. Statistical tests will be performed using two-sided significance levels of 5% unless otherwise specified. Statistical analysis will be conducted with R version 3.6 or higher.

10.3.2 Analysis of the Primary Effectiveness Endpoint

Agreement of DCTclock-pen and DCTclock-tablet in assessing cognitive impairment will assess by using the Bland-Altman method. The following hypothesis test will be carried out:

H0: $Lower_{LoA} \leq -\delta \ or \ Upper_{LoA} \geq \delta$

H1: $-\delta < Lower_{LoA} < Upper_{LoA} < \delta$

where δ = 30 is the pre-specified maximum allowable difference, $Lower_{LoA}$ is the lower bound of the two-sided 95% limits of agreement (LoA), $Upper_{LoA}$ is the upper bound of the two-sided 95% LoA. The conclusion that the two measurements are in agreement (i.e. equivalent) depends on whether the two-sided 95% confidence intervals of each (lower, upper) limit of agreement are within the boundaries set from the maximum allowable difference.

Specifically, Bland-Altman analysis will consist of the following:

1. Calculate the paired difference in scores between the two tests (i.e. Discrepancy scores) for each participant.
2. Calculate the mean of these paired differences.
3. Calculate the average of the two test results for each participant.
4. Plot the paired differences (y-axis) vs. the average of the two test results (x-axis). This is commonly called the Bland-Altman plot.
5. Calculate a two-sided 95% limits of agreement (LoA) of the paired differences as: mean difference +/- 1.96*standard deviation of the differences.
6. Calculate two-sided 95% confidence interval of each (lower, upper) limit of agreement.
7. The conclusion that the two measurements are in agreement (i.e. equivalent) depends on whether the confidence intervals constructed from the data are within the boundaries set from the maximum allowable difference.

In addition to the above primary analysis, the following additional agreement analyses between DCTclock-tablet and DCTclock-pen scores will be conducted using the DCTclock overall score as well as the scores from the Composite Scales (Drawing Efficiency, Information Processing, Simple and Complex Motor, and Spatial Reasoning):

- Perform the Bland-Altman analysis on the scores from the composite scales.
- DCTclock-tablet scores will be plotted against DCTclock-pen scores in a scatter plot, superimposed with a line of identity.
- An unweighted Deming regression (where the variance of the measurement error for each of DCTclock-pen and DCTclock-tablet is determined by the two measurements that were collected 3-5 weeks apart) will be carried out to determine the y-intercept, slope and their two-sided 95% confidence intervals.
- The intraclass correlation coefficient (ICC) will be calculated
- Root mean squared differences (RMSD), the square root of the average squared discrepancy score, will be calculated to indicate the average amount by which scores differ.
- Mean differences will be compared using paired *t*-tests for equivalence, where lower and upper equivalence limits are -30 and 30, respectively.

10.3.3 SAMPLE SIZE

The primary null and alternative hypotheses are:

H0: $LCI_{LLoA} \leq -\delta \ or \ UCI_{ULoA} \geq \delta$

H1: $-\delta < LCI_{LLoA} < UCI_{ULoA} < \delta$

where δ = 30 is the pre-specified maximum allowable difference, LCI_{LLoA} is the lower bound of the two-sided 95% confidence interval for the lower bound of the two-sided 95% limits of agreement (LoA), UCI_{ULoA} is the upper bound of the two-sided 95% confidence interval for the upper bound of the two-sided 95% LoA.

The primary endpoint will be analyzed using Bland-Altman method. This study will produce limits of agreement (LoA) and associated confidence intervals from the two measurements on each subject. The conclusion that the two measurements are in agreement (i.e. equivalent) depends on whether the confidence intervals constructed from the data are within the boundaries set from the maximum allowable difference. An evaluable sample size of 41 subjects achieves at least 90% power to detect agreement when the confidence level of the LoA is 95%, the confidence level of the confidence intervals about the LoAs is 95%, and the maximum allowable difference is 30. The mean and standard deviation of the sample differences are anticipated to be 10 and 7, respectively.

Accordingly, approximately 175 participants will be enrolled in order to obtain a DCTclock-tablet training dataset of at least 100 participants and a DCTclock-tablet validation dataset of greater than 41 evaluable subjects.

10.3.4 EXPLORATORY ENDPOINTS

10.3.4.1 AGREEMENT WITH MMSE AND RBANS

Linus Platform individual tests will be compared to MMSE and RBANS to measure agreement in assessment of cognitive status in the validation dataset. Additionally, Linus Platform individual tests will be combined to obtain a Linus overall score (Linus score) to measure cognitive status: the training dataset will be used to create a Linus score based on the individual Linus Platform tests and the validation dataset will be used to validate the Linus score by assessing its agreement with MMSE and RBANS.

For each pairing of the individual Linus Platform scores or the developed Linus score and the reference standard MMSE and RBANS (Reference score), agreement analyses will be carried out as follows:

- To better visualize the relationship between the two tests, the Linus score and will be plotted separately against the Reference score 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.

10.3.4.2 TEST-RETEST RELIABILITY

Participants will undergo cognitive testing with both the Linus Platform tests and the reference standard RBANS twice, where the second examination will be three to five weeks after the first examination. Test-retest reliability of both individual Linus Platform tests and the combined Linus score will be

compared to the test-retest reliability of the RBANS. For the analysis, participants who no longer satisfy the inclusion/exclusion criteria prior to the second examination will be excluded.

For, the individual Linus Platform scores, the developed Linus score, and the reference standard RBANS, agreement analyses will be carried out as follows:

- Agreement between the first and second measurements will be measured. A scatter plot of measurement 2 vs. measurement 1 will be generated, superimposed with a line of identity. An unweighted Deming regression (where the variance of the measurement error is determined by the two measurements that were collected 3-5 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.

10.3.5 Safety Analyses

Safety analysis will be performed on the DCTclock and Linus Platform safety analysis dataset. Treatment emergent adverse events, which are events that started or worsened during or after the first DCTclock or Linus Platform test, will be listed including start date of event and date and time of the test. The number of serious device related adverse events and number and percentage of subjects with at least one serious device related adverse event will be presented for each test.

10.3.6 Planned Interim Analyses

There is no formal interim analysis for the study. Enrollment and screening results will be reviewed routinely to ensure subjects with a range of cognitive function are represented in the study population.

10.3.6.1 Effectiveness Review

There will be no review of effectiveness at the interim.

10.3.6.2 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.

10.3.7 Multiple Comparison/Multiplicity

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

10.4 Measures to Minimize Bias

10.4.1 Enrollment/ Randomization/ Masking Procedures

Blocked randomization of subjects into group 1 and 2 will be used. Subjects will be randomized immediately prior to the visit 1 DCTclock test. A block size of 4 will be used. The allocation ratio will be 1:1 to obtain the same number of subjects per group.

10.4.2 Evaluation of Success of Blinding

N/A

10.4.3 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 Belmont Report 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 study staff 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 site emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

As subjects with varying levels of cognitive impairment will be recruited for this trial, steps will be taken to ensure that a subject's cognitive status does not impact their ability to consent. Several studies have considered and discussed competency and capacity to consent to research among older persons and those with dementia (19) (20). In agreement with those studies, patients with a previously documented MMSE or Montreal Cognitive Assessment (MoCA) score $\leq$ 18 or who receive a score of 18 or less on the MMSE given during screening will be excluded from the study or required to have a legally authorized representative consent to the study.

For participants with a previously documented MMSE or MoCA score >18 or without a historical score, all attempts will be made to ensure that the participant understands the study including asking them three questions about the study after the consent discussion (how many visits are there, how long do the study visits last, and how much will you be paid). A screening MMSE will also be conducted. If, based on an inability to correctly answer these questions, a subject is not capable of providing consent due to their lack of understanding of the study details, they will be excluded from the study unless consent can be obtained from a legally authorized representative. As noted above for those who do consent and progress to screening, an MMSE score $\leq$18 on the screening MMSE administered during the study is also exclusionary. Any subject excluded due to the screening MMSE, can be re-enrolled in the study if a legally authorized representative consents.

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) 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. 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.

Study participant research data from DCTclock and the Linus Platform tests will be transmitted to the sponsor or their partners as outlined below. This data will not include the participant's contact information. Rather, individual participants and their research data will be identified by a unique study identification number.

DCTclock (tablet and pen) and Linus platform drawing tasks- Data from these tests includes time-stamped coordinate level details of the drawing process. It is encrypted at the time of collection (either on the digital pen or iPad) and transmitted by way of a locally installed data transfer application directly to the sponsor's HIPAA compliant servers, at which point they are deleted from the input device (tablet or pen).

Linus Platform reaction time and gait assessments- Data from these tasks includes millisecond-level precise measurements of reaction time to tablet screen stimuli as measured by the tapping of buttons on the tablet (reaction time) and gyroscope and accelerometer readings collected on a smartphone (gait). These measurements are stored locally on the tablet/smartphone with encryption before transmission directly to the sponsor's HIPAA compliant servers, at which point they are deleted from the device.

Linus Platform Lifestyle questionnaire and PHQ-9- Data from these tasks include fixed 'yes/no' and 'not at all/several days/more than half the days/nearly every day' answers to questions presented to the participant on the tablet. These responses are stored locally on the tablet with encryption before transmission directly to the sponsor's HIPAA compliant servers, at which point they are deleted from the device.

Linus Platform speech analysis- Speech recordings and meta data about the speech session are stored locally on the tablet with encryption until they are successfully uploaded to the sponsor partner's HIPAA compliant web servers, at which point they are deleted from the device. The data is encrypted in transit and at rest on the servers. All data is hosted on AWS behind secure API gateways and is access-controlled so that only trained and approved employees can access it. Meta data only includes non-identifying information, such as time & date for the session and information about the study supplied tablet device. Audio is also sent to a HIPAA compliant transcription provider for transcription. The resulting raw audio samples, transcripts, and analysis of the voice recording transferred to the sponsor will include details such as phonation and respiratory control.

Linus Platform eye tracking-based memory assessment- Full face video recordings will be captured on a tablet and encrypted for storage. All videos will be stored locally at the study site. De-identified video files will be transmitted by way of a locally installed data transfer application to the secure server of a sponsor partner for analysis. No other participant details will be shared with the third party. The resulting analysis of the video recordings shared with the sponsor will include de-identified video files, gaze times and other eye movement parameters.

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.

18 LITERATURE REFERENCES

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Version Information

Version	Date	Significant Revisions
1	7/29/20	N/A
2	9/9/20	Addition of exploratory endpoints and a statistical description for the exploratory endpoints, clarification of safety endpoints to include that they will be analyzed and reported per test, the addition of a Linus Platform lifestyle questionnaire, a change in subject compensation, clarification of language regarding the regulatory status of DCTclock-pen, and minor editorial changes.
3	10/12/20	Addition of a new speech and voice assessment (list learning) which is administered at both visits.
4	1212/23	Update address and contact information