Philips Research

PHILIPS



# Clinical Study Investigation Plan

## PJ-011726 Study to establish the psychometric properties of the digital cognitive tests on the Philips IntelliSpace Cognition Platform

| Document history | | | |
|---|---|---|---|
| Version: | Date: | Author: | Description/Change/Reason for Change |
| *0.1* | *09-08-2017* | *Laura Klaming, Ben Schmand* | *1st version* |
| *0.2* | *24-08-2017* | *Daisy van Minde* | *2nd version* |
| *0.3* | *07-03-2018* | *Laura Klaming, Ron Dotsch* | *3rd version* |
| *0.4* | *18-09-2018* | *Laura Klaming, Ben Schmand* | *4th version* |
| *0.5* | *04-10-2018* | *Daisy van Minde, Murray Gillies* | *5th version* |
| *0.6* | *07-11-2018* | *Ron Dotsch, Ben Schmand, James Holdnack, Justin Miller, Daisy van Minde* | *6 th version* |
| 0.7 | *14-11-2018* | *Mandy Spaltman* | *New template and few additions* |
| 0.8 | *16-11-2018* | *Daisy van Minde* | *8th version* |
| 0.9 | *29-11-2018* | *Daisy van Minde* | *9th version* |
| 0.10 | *06-12-2018* | *Mandy Spaltman* | *Minor changes after ICBE secretary review* |
| 0.11 | *13-12-2018* | *Mandy Spaltman* | *Minor changes after ICBE review* |
| 0.12 | *14-12-2018* | *Daisy van Minde* | *Comments after pre-review ICBE and from Q&R addressed. Final draft before ICBE Board review* |
| 0.13 | *19-12-2018* | *Gert-Jan Adriaans* | *Added definition 'norm data' to chapter 3 as it is the main purpose of study and reflecting to privacy assesment.* |
| 0.14 | *19-12-2018* | *Mandy Spaltman* | *Slight rephrasing of norm data definition.* |
| 1.0 | *21-12-2018* | *Mandy Spaltman* | *Removing markup for approved version.* |

| | | | |
|---|---|---|---|
| 2.0 | *18-02-2019* | *Mandy Spaltman* | *Edit to our sample size.* |

## APPROVAL / PROTOCOL SIGNATURE SHEET

| Function | Name | Signature /Date (yyyy-mmm-dd) |
|---|---|---|
| **Regulatory Representative of Sponsor** Sr. Q&R Manager Philips HealthWorks, Business Excellence | Marta Walker | 2019-04-02 |
| **Principal Investigator** | James Holdnack | 2019-03-29 |

## ROLES / RESPONSIBILITIES

This section contains a list of all parties and persons involved in the Clinical Investigation.

| | |
|---|---|
| **Coordinating investigator/ Project leader** | Daisy van Minde<br>High Tech Campus 34.1.038<br>5656 AE Eindhoven, the Netherlands<br>Tel: +31646802217<br>Email: daisy.van.minde@philips.com |
| **Principal investigator(s)** | James Holdnack<br>5 Rose Hill Drive, Bear DE 19701<br>U.S.A<br>Tel: +1(302) 312-4077<br>Email: james.holdnack@philips.com |
| **Investigational Site** | N/A |
| **Other participating sites** | Several office rooms will be rented in the USA to conduct the study. |
| **Sponsor (the individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation)** | Philips Electronics Nederland B.V.,<br>acting through its Philips HealthWorks organization<br>High Tech Campus 34<br>5656 AE Eindhoven, The Netherlands |
| **Subsidizing party** | N/A |
| **Independent physician(s) (the Netherlands only)**** | N/A |
| **Laboratory sites** | N/A |
| **Co-investigators** | |
| • Roel Cuppen – Senior Architect<br>• Mandy Spaltman – Psychologist Researcher<br>• Gijs van Elswijk – Cognitive Scientist<br>• Ron Dotch – Cognitive Psychologist/ Data scientist<br>• Stefan Vermeent - Psychologist/ Data scientist<br>• Ben Schmand – Professor in Clinical Neuropsychology | |
| **Appendix** | |
| • A. Sampling plan<br>• B. Validation ISC – device list | |

# TABLE OF CONTENTS

## LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

| | |
|---|---|
| ABR | ABR form, General Assessment and Registration form, is the application form required for submission to the accredited Ethics Committee<br>*In Dutch, ABR = Algemene Beoordeling en Registratie* |
| AE | Adverse Event<br>Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device |
| AR | Adverse Reaction |
| CA | Competent Authority |
| Clinical Investigation | Systematic investigation in one or more subjects, undertaken to assess the safety and performance of a medical device |
| CIP | Clinical Investigation Plan<br>Document that state(s) the rationale, objectives, design and proposed analysis, methodology, monitoring, conduct and record-keeping of the clinical investigation<br>NOTE: The term "protocol" is synonymous with "CIP". However, protocol has many different meanings, some not related to clinical investigation, and these can differ from country to country. |
| CFA | Confirmatory factor analyses |
| CFR | Code of Federal Regulations |
| CNS | Central Nervous System |
| COWAT | Controlled Oral Word Assocation Test |
| CRF | Case Report Form<br>Set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the CIP |
| CV | Curriculum Vitae |
| DCDx | Digital Cognitive Diagnostics |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| ECT | Electroconvulsive therapy, |
| EDC | Electronic Database Capture |
| Endpoint | Principal indicator(s) used for assessing the primary hypothesis of a clinical investigation |
| EU | European Union |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HCP | HealthCare Professional |
| HSDP | HealthSuite Digital Platform (Philips) |
| Hypothesis | Testable statement, resulting from the objective, regarding the investigational medical device safety or performance used to design the clinical investigation and that can be accepted or rejected based on results of the clinical investigation and statistical calculations.<br>NOTE: The primary hypothesis is the determinant of the investigational medical device safety or performance parameters and is usually used to calculate the sample size. Secondary hypotheses concerning other points of interest can also be evaluated. |
| ADL | Activity of Daily Living |
| IB | Investigator's Brochure |
| IC | Informed Consent<br>The informed consent is documented by means of a written, signed and dated informed consent form.<br>The informed consent process is the process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation. |
| ID | Identification |
| IRB | Institutional Review Board |
| ISC | IntelliSpace Cognition |

| | |
|---|---|
| Investigator | Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation- related decisions.<br>NOTE: An individual member of the investigation site team can also be called "sub-investigator" or "co-investigator". |
| MMSE-2 | Mini Mental Status Exam 2 |
| MoCA | The Montreal Cognitive Assessment |
| Objective | Main purpose for conducting the clinical investigation |
| Point of enrollment | Time at which, following recruitment, a subject signs and dates the informed consent form |
| QMS | Quality Management System |
| ROCFT | Rey Osterrieth Complex Figure Test |
| SAE | Serious Adverse Event<br>Adverse event that<br>a) led to death,<br>b) led to serious deterioration in the health of the subject, that either resulted in<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, or<br>3) in-patient or prolonged hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) led to foetal distress, foetal death or a congenital abnormality or birth defect<br>NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event. |
| Sponsor | Individual or organization taking responsibility and liability for the initiation or implementation of a clinical investigation |
| TBI | Traumatic Brain Injury |
| TMT | Trail Making Test |
| USA | United States of America |

# 1 1 EXECUTIVE SUMMARY

| | |
|---|---|
| **Study Title & ID** | PJ-011726 Psychometric properties of IntelliSpace Cognition<br><br>Full title: Study to establish the psychometric properties of the digital cognitive tests on the Philips IntelliSpace Cognition Platform |
| **Project Name** | N/A |
| **Brief Summary of Study**<br>***Provide a lay-language abstract of your study plan (100-300 words)*** | This study aims to validate the tests that are on the IntelliSpace Cognition platform and to establish normative data for these tests. |
| **Key Words Associated with Study**<br>**Provide 3-5 PubMed MeSH keywords** | Cognitive model<br>Cognitive assessment<br>Digital cognitive tests<br>Automated scoring<br>Algorithms |
| **Country(s) from where the data originates (where collected)** | ☐ Netherlands ☒ USA ☐ Germany ☐ China<br>☐ India ☐ Belgium ☐ UK ☐ Kenya<br>☐ Other: |
| **ISO 14155 compliance** | ☒ This study will be conducted per the requirements of ISO 14155<br>☐ This study WILL NOT be conducted per the requirements of ISO 14155. For example studies formerly known as H-lite and J-Lite<br><br>This study has no clinical primary or secondary objectives. However the data generated from this study will be used as ground data in a Device class II according to regulation CFR21 Sec. 882.1470 Computerized cognitive assessment aid.<br><br>Therefore Philips will follow ISO 14155, Good Clinical Practice in all applicable requirements.<br><br>Data generated from this trial will be monitored and will be Part 11 compliant.<br><br>Important note 1: There are no foreseeable risks or possible adverse events in this study. This is a non-significant risk study .<br><br>The study will be submitted to ICBE and IRB review /approval. |
| **Is this study part of a student project/thesis?** | ☒ No<br>☐ Yes, Student Name: University: |
| **Primary objective** | The study has four aims. |

| | |
|---|---|
| | 1. To compare the psychometrics of digital and paper-pencil cognitive tests. Score distributions, test-retest reliability, and construct validity of the following tests will be compared: Trail Making Test (TMT), Rey Osterrieth Complex Figure Test (ROCFT), Digit Span Test, Controlled Oral Word Association Test (COWAT), Category Fluency Test, Rey Auditory Verbal Learning Test (RAVLT), Clock Drawing Test, Star Cancellation Test, O Cancellation Test, Mini Mental Status Exam 2 (MMSE-2).<br><br>2. To assess the degree of agreement between the algorithm and manual scores for the digital Rey Osterrieth Complex Figure Test and Clock Drawing Test.<br><br>3. To estimate regression-based norms and reliable change indices.<br><br>4. To estimate factor loadings for a structural equation model describing cognition in terms of distinct cognitive domains |
| **Secondary objective(s)** | The secondary objective of the study is to explore usability aspects of IntelliSpace Cognition. |
| **Participating parties and their roles** | Sponsor: Philips Electronics Nederland B.V.,<br>• Internal Ethics approval<br>• Providing Principal Investigator<br>• Study Design<br>• Monitoring<br>• Data storage<br>• Data integrity check<br>• Data analysis<br>• Report<br>Study co-ordinator:<br>• Selection of rooms for data collection<br>• Selection of psychometrists<br>• IRB approval<br>• Recruitment of participants<br>• Data collection |
| **Subjects** | The study will include at minimum *N*=400 and up to *N*=450 healthy participants who will be sufficiently distributed across gender, ages 55 to 80 for validation data and ages 50 to 80 for normative data, ethnicity, and education level to reflect the distribution of people that will typically be assessed with IntelliSpace Cognition.<br><br>As this study is in preparation of selling a reliable product, we aim to obtain norms based on a sample that adequately reflects the US population.<br><br>A variety of standard techniques will be used to recruit participants. |

| | |
|---|---|
| | **Inclusion Criteria:**<br><br>• Examinee's primary language (language most often spoken) must be English.<br>• If examinee has vision impairment or hearing loss, must be corrected to normal.<br>• Must have normal fine and gross motor ability<br>• Must have use of fingers, hands, and arms to be able to use a pencil to write symbols.<br>• Must be able to understand subtest instructions and participate fully in testing. |
| | **Exclusion Criteria:**<br><br>• Evidence of current cognitive impairment.<br>• Disruptive behavior or insufficient compliance with testing to ensure a valid assessment.<br>• Examinee must not be currently admitted to a hospital, assisted living, nursing home or a psychiatric facility.<br>• Examinee must not be diagnosed with a neurological disorder or disease (e.g., Parkinson's, brain tumor, stroke, TBI, epilepsy [if # seizures ≤ 2 and not receiving ongoing treatment for seizures, and not currently seeking medical evaluation or attention related to seizures, examinee can be accepted], encephalitis, dementia, language disorder (expressive or mixed receptive/expressive excluded; articulation disorder is ok), learning disorder.<br>• Must not have been unconscious related to traumatic brain injury or "medical condition" > 20 minutes (however, e.g., heat stroke, medication induced are ok) or any head-injury resulting in an overnight hospital stay.<br>• Any history of a medical event requiring resuscitation in which examinee was non-responsive for > 15 minutes.<br>• Must not have current or recent functional change (ability to carry out usual duties at work, in school, IADLs [driving, shopping, managing money], etc.) due to cognitive change.<br>• Examinee must not be receiving chemotherapy treatment, or have received chemotherapy treatment in the past 2 months.<br>• Examinee must not have a history of ECT or radiation to the CNS.<br>• Examinee must not be (currently or in the past) diagnosed with a psychotic disorder, or currently diagnosed with a mood disorder (however, Major Depressive Disorder in remission or with no current episode, and Dysthymic and Adjustment Disorders, are acceptable) or an anxiety disorder with symptoms significant enough to interfere with optimal test performance.<br>• Autoimmune disorder (e.g., LUPUS, Multiple Sclerosis)<br>• Examinee must not be currently diagnosed with substance abuse or dependence, or have carried any substance abuse or dependence diagnosis in the past year (> 1 year in remission diagnoses are ok). Long term alcohol abusers are excluded as well (e.g., abused substance for more than 10 years).<br>• Any history of Autism Spectrum Disorder or Intellectual Disability. |

| | |
|---|---|
| | • The examinee must not be currently taking medication that might impact test performance (e.g., anti-convulsants, antipsychotics, benzodiazepines, psychostimulants, opiods, tricyclic antidepressants, some norepinephrine reuptake inhibitors). Most antihypertensive medications and statins are acceptable.<br>• If previously diagnosed with any physical condition or illness that might depress test performance, illness must not interfere with normal cognitive functioning at work, school, ADLs, etc. Diabetes, hypothyroidism, and hypertension are acceptable if controlled.<br>• Exclude primarily nonverbal or uncommunicative. Must not have a diagnosis of aphasia.<br>• Examinees should not have received neuropsychological testing although previous MMSE testing is allowed if more than 6 months prior<br>• Examinee must not be seeking medical diagnostic procedures for cognitive difficulties from a medical professional.<br>• Non-valid health insurance in USA. |
| **Investigation design** | The study has a randomized, counterbalanced design with two conditions to which participants will be assigned randomly with minimization for demographic variables. |
| **Investigation procedures** | The study consists of two phases. All participants in phase 1 will be invited to participate in two assessments that will take place with a time interval of two weeks between the two time points to minimize retest effects. Participants (total $N$ = 400) will be randomly assigned to one of the following groups:<br><br>- Group A ($n$=100) completes digital tests in phase 1 and paper-pencil tests in phase 2,<br>- Group B ($n$=100) completes paper-pencil tests in phase 1 and digital tests in phase 2,<br>- Group C ($n$=50) completes digital tests in both phases,<br>- Group D ($n$=50) completes paper-pencil tests in both phases,<br>- Group E ($n$=100) only completes digital tests in one phase (50% of group E will be enrolled in phase 1 and the other 50% of group E will be enrolled in phase 2).<br><br>If the timeline allows for it, up to 50 additional participants aged 50-54 will be included in group E to stretch the age range for the regression-based norms, making the group size up to $n$=150 and the total sample size up to $N$ = 450.<br><br>The data of group A and B are used to compare score distributions within-subjects.<br><br>The data from groups A-D (phase 1) are used to compare score distributions between-subjects (aim 1). |

| | |
|---|---|
| | The data of group C and D are used to assess and compare test-retest reliability (aim 1) and assess reliable change indices (aim 3).<br><br>The data of group A (phase 1), group C (phase 1) and group E are used to estimate regression based norms for the digital tests (aim 3), as well as to estimate factor loadings for the structural equation model (aim 4).<br><br>The data of group A (phase 1), group B (phase 1), group C (phase 1) and group D (phase 1) are used to compare construct validity (aim 1).<br><br>Participants will be randomized with minimization for demographic variables (gender, age, education level, ethnicity).<br><br>Assuming a dropout rate of 20% we will oversample our desired N by the same percentage, resulting in sampling of 480 participants.<br><br>The completed tests will be scores by two well-trained raters, with double scoring of 30% of participants to assess inter-rater agreement.<br><br>Scoring algorithms for the ROCFT and the Clock Drawing Test are applied post-data collection. The scores estimated by the algorithms will be compared with manual scoring by a sample of well-trained raters ($n$ = 6; aim 2). The data collected during this study are only used for validation and not used in any way to train these scoring algorithms.<br><br>Each assessment will last approximately 1.5 hours. |
| **At-Home Subject Procedures** | ☒ NOT APPLICABLE |
| **Devices**<br><br>**Check each box as appropriate and add a brief description of the device(s)—e.g., fitness tracker, VR goggles, breast pump, electric toothbrush, ELAN, MRI scanner.**<br><br>**Devices will be described fully in Section 2.1 of the study protocol.** | ☐ None<br>☐ Mock-up (see ICBE FAQ definition):<br>☒ Survey/questionnaire (if copyrighted, ensure permission for use):<br>Usability questionnaire<br>☐ Interview/focus group with audio/video taping**:<br>☐ Interview/focus group without audio/video taping**:<br>**see decision flowchart regarding interviews vs QI vs consulting https://share-intra.philips.com/sites/STS20131115093003/ICBE-FAQ/Lists/Photos/interviews%20criteria%20flowchart%20feb2018.pptx<br>☐ FDA or CE-approved medical device within intended use:<br>☐ FDA or CE-approved medical device outside intended use:<br>☒ FDA or CE-approved non-medical device within intended use:<br><br>  <br><br>The digital tests will be provided to the |

| | |
|---|---|
| | participants on an Ipad Pro (Apple). It has a screen size of 12.9-inch with a screen resolution of 2732×2048. Participants will use the Apple pencil for the Ipad Pro to perform the tests (see Figure). Both the iPad Pro as well as the Apple Pencil are wiped clean after use by each participant.<br><br>To digitally administer the digital tests to the participants, the test leader will start the test via the software prototype on a regular laptop that will be provided by Philips (see Figure).<br><br>The Ipad pro, Apple pencil and the regular laptop will all be commercially available devices and used within their intended use.<br><br>☐ FDA or CE-approved non-medical device outside intended use:<br>☐ In vitro medical device:<br>☐ Medical device prototype***:<br>☐ Non-medical device prototype***:<br>☒ Software prototype***, non-medical:<br><br>A selection of the digital tests are administered to the participants via a software prototype designed by Philips (Production Equivalent Device).<br><br>☒ Software prototype***, medical:<br><br>A selection of the digital tests is administered to the participants via a medical software prototype (on an iPad) designed by Philips (IntelliSpace Cognition).<br><br>☐ Other:<br><br>***Before a study employing prototypes may start, a Declaration of Conformity (DoC) needs to be issued by the Director Regulatory Affairs. With this DoC, Philips declares that the device can safely be used in the study. It may be needed to work according to some formal standards to build up this evidence (e.g. with respect to bio-compatibility or sterility).<br><br>***☐ DoC needed (brief overview of the actions that will be taken to get the Declaration of Conformity. See Philips Research QMS procedure "Procedure Product Release (QR-PRO-36". Give details of how the project will deal with the regulatory requirements. Consult the Q&R office when needed): |
| **Milestones** | ICBE review will be completed 17 December 2018<br>IRB review will be completed 15 Feb 2019<br>Data collection will start in 15 March 2019<br>Data collection for time point 1 will be completed 15 June 2019 (with four examiners)<br>Data collection for time point 2 will be completed 15 Sept 2019 (with four examiners)<br>Data analysis will be completed 15 October 2019<br>Report will be completed 15 October 2019 |
| **Claims** | Will you obtain regulatory (FDA, CE) approval for a new product or service, a new indication, or a new marketing claim?<br>☐ Yes ☒ No N/A 510K exempt |

| | |
|---|---|
| | If YES, in what countries will the claims be registered?<br>☐ Netherlands ☒ USA ☐ Germany ☐ China<br>☐ India ☐ Belgium ☐ UK ☐ Kenya<br>☐ Other:<br><br>Have you developed a list of claims that you would like to assert for your product or service? ☒ Yes ☐ No |
| **External Research Ethics Committee (REC) Approval**<br>**Note: if your document is not in English or Dutch, include an English translation** | ☐ Not Required (not a local/state/country requirement)<br>☒ Required (apply for it AFTER ICBE approval)<br>☐ Approval already obtained (upload for review by ICBE)<br>☐ REC Review is waived (upload review waiver)<br>☐ REC has waived requirement for informed consent (upload waiver)<br>☐ Check this box if more than one REC is involved in this study and identify them: |
| **Submission to Competent Authorities** | ☒ Not applicable (510K exempt)<br><br>Check the applicable option concerning Competent Authority approval for medical device studies:<br>☐ No submission to Competent Authority needed, since no non-released medical device involved<br>☐ Approval from Competent Authority is mandatory for this study with a non-released medical device<br><br>Note: Released medical device means a device that is e.g. CE-marked (93/42/EEC) if study takes place in EU, or has 510k if study takes place in USA.<br><br>Our device will be marketed as a Class-II Medical Device in the US. The device is 510(k) exempt by the FDA.<br>Link:https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?id=3768 |
| **Database registration** | ☐ None<br>☒ ClinicalTrials.gov<br>☐ Other: |
| **Type of Legal Agreement for this study** | ☐ None required ☐ MRA Exhibit<br>☒ Contract ☒ Purchase Order<br>We will work with a CRO (supplier) via a purchase order and additional CRO agreement |
| **Status of Legal Agreement** | ☐ NA ☐ Not started ☒ In Process ☐ In Place<br>Name of Legal Rep: Jennifer Nene |
| **IP Strategy** | See CRO agreement |
| **ICBE Training is required for all key study personnel** | ☒ YES, this training is completed as required by ICBE*<br>☐ NO, this training is not completed as required by ICBE*: |

# 2 INVESTIGATIONAL DEVICE

## 2.1 Device Summary

This chapter contains a summary description of the **investigational device** and its intended purpose.

| | |
|---|---|
| **Summary device description** | Philips IntelliSpace Cognition (ISC) is a digital proposition from the Digital Cognitive Diagnostics (DCDx) venture. It is a digital aid which supports HealthCare Professionals (HCPs) in assessing the cognition of individuals within a healthcare facility. It consists of two interfaces connected to the DCDx-module in the cloud. ISC will be hosted on the Health Suite Digital Platform (HSDP). The first interface is the patient's interface and is presented via a tablet to collect data on how the patient performs a series of tests. The second interface is the clinician's interface and is typically located on a laptop. It allows for tests or test batteries to be selected, observations noted, data analytics performed and the generation of a report. Philips ISC is a Class-II Medical Device in the US and provides objective data regarding cognition via scoring algorithms that HCPs can use to inform diagnostic decision making and treatment planning. It enables tracking cognition over time and offers the possibility of new outcome measures. ISC can be used in a variety of healthcare environments such as neurology and neuropsychology practices.<br><br>In this study 4 devices/tools will be used:<br>• A version of the ISC medical product (as engineered in accordance with the HealthWorks QMS) and that is verified to be used for data collection and provides the interface of the final product for the tests: TMT, Clock Drawing Test, MMSE-2, ROCFT, and Digit Span Test.<br>• A production equivalent (research platform) that provides: O Cancellation Test, Category Fluency Test, RAVLT, COWAT and Star Cancellation.<br>• Paper tests: Trail Making Test, Rey Osterrieth Complex Figure Test, Digit Span Test, Controlled Oral Word Association Test, Category Fluency Test, Rey Auditory Verbal Learning Test, Clock Drawing Test, Star Cancellation Test, O Cancellation Test, MMSE-2. In addition a naming test in paper format will also be included.<br>• A MoCA paper based screener test.<br><br>In this study, these devices/tools will be used to investigate score distributions, construct validity and test-retest reliability. |
| **Summary intended purpose** | The IntelliSpace Cognition tool is intended to be used as an adjunctive tool in the assessment of an adults' level of cognitive functioning.<br><br>The IntelliSpace Cognition tool provides health care professionals with an overview of both the overall cognitive performance as well as specific cognitive domains.<br><br>The IntelliSpace Cognition tool provides health care professionals with a method to compare a person's cognitive performance over different assessments (moments in time). |

| | |
|---|---|
| | The results from IntelliSpace Cognition tool are intended to be used by healthcare professionals who have participated in IntelliSpace Cognition trainings.<br><br>The data collected by IntelliSpace Cognition are intended to be collected under the supervision of a HCP.<br><br>The IntelliSpace Cognition tool is not intended as a stand-alone or adjunctive diagnostic device.<br><br>The assessments provided via the IntelliSpace Cognition tool may be used for a wide variety of patient groups, as well as healthy individuals when a HCP wishes to gain more insight into cognitive performance.<br><br>Disclaimer:<br>• The cognitive model of IntelliSpace Cognition tool has been scientifically validated for assessing the cognition of healthy people in the age group of 55-80.<br>• The IntelliSpace Cognition tool has not been validated for use with adults under the age of 55 or over the age of 80 and doesn't include normative data for adults under the age of 50 or over the age of 80. |
| **Population description** | The tests provided via the IntelliSpace Cognition may be used for anyone where an overview of cognitive functioning is required provided they are part of the demographic group as described in the section titled "subjects". |
| **Manufacturer** | The legal manufacturer is Philips HealthWorks for which FDA 21 CFR 820.30 compliant design control will be implemented to allow for clinical validation of the device as part of 21 CFR 820.12 Investigational Device Exemptions. |
| **Device model/type** | A released version of the ISC product (as engineered in accordance with the HealthWorks QMS) and that is verified to be used for data collection and provides the interface of the final product for the tests: TMT, Clock Drawing Test, MMSE-2, ROCFT and Digit Span Test.<br><br>A production equivalent (research platform) that provides: O Cancellation Test, Category Fluency Test, RAVLT, COWAT and the Star Cancellation. |
| **Software version** | Software version 1.0.0 of the ISC product will be released for the clinical investigation.<br><br>Software version 3.10.6A of the product equivalent will be used for the clinical investigation. |
| **Accessories** | iPad Pro tablets (Apple)<br>Apple pencils<br>Regular laptops |
| **Traceability procedure** | Maintenance of the device will be carried out by Philips employees. Cleaning of the device will be carried out as needed by the investigators. When the device is not used for the clinical investigation it is placed inside a locked cabinet in a locked office at the sites. At clinical investigation termination or |

| | |
|---|---|
| | closure, the device will be returned to Philips and checked by the Monitor. The devices, SW and accessories are uniquely identified and listed in appendix B Validation ISC – device list. |
| **Required training** | Persons qualified to administer the neuropsychological tests, i.e. a psychologist or psychometrist, will use the investigational devices to collect data as part of the clinical investigation. Employees of Philips will train the researchers for operation of the investigational devices. |
| **Specific procedure acts** | N/A |
| **Device Labeling** | The software will contain a label with the text; not for clinical use. |

## 2.2 Intended purpose

The IntelliSpace Cognition tool is intended to be used as an adjunctive tool in the assessment of an adults' level of cognitive functioning.

The IntelliSpace Cognition tool provides health care professionals with an overview of both the overall cognitive performance as well as specific cognitive domains

The IntelliSpace Cognition tool provides health care professionals with a method to compare a person's cognitive performance over different assessments (moments in time).

The results from IntelliSpace Cognition tool are intended to be used by healthcare professionals who have participated in IntelliSpace Cognition trainings.

The data collected by IntelliSpace Cognition are intended to be collected under the supervision of a HCP

The IntelliSpace Cognition tool is not intended as a stand-alone or adjunctive diagnostic device.

The assessments provided via the IntelliSpace Cognition tool may be used for a wide variety of patient groups, as well as healthy individuals when a HCP wishes to gain more insight into cognitive performance.

Disclaimer:

- The cognitive model of IntelliSpace Cognition tool has been scientifically validated for assessing the cognition of healthy people in the age group of 55-80
- The IntelliSpace Cognition tool has not been validated for use with adults under the age of 55 or over the age of 80 and doesn't include normative data for adults under the age of 50 or over the age of 80.

## 2.3 Device Description

Philips IntelliSpace Cognition (ISC) is a digital proposition from the Digital Cognitive Diagnostics (DCDx) venture. It is a digital aid which supports HealthCare Professionals (HCPs) in assessing the cognition of individuals within a healthcare facility. It consists of two interfaces connected to the DCDx-module in the cloud. ISC will be hosted on the Health Suite Digital Platform (HSDP). The first interface is the patient's interface and is presented via a tablet to collect data on how the patient performs a series of tests. The second interface is the clinician's interface and is typically located on a laptop. It

allows for tests or test batteries to be selected, observations noted, data analytics performed and the generation of a report. Philips ISC is a Class-II Medical Device in the US and provides objective data regarding cognition via scoring algorithms that HCPs can use to inform diagnostic decision making and treatment planning. It enables tracking cognition over time and offers the possibility of new outcome measures. ISC can be used in a variety of healthcare environments such as neurology and neuropsychology practices.

In this study 4 devices/tools will be used:

- A version of the ISC medical product (as engineered in accordance with the HealthWorks QMS) and that is verified to be used for data collection and provides the interface of the final product for the tests: TMT, Clock Drawing Test, MMSE-2, ROCFT, and Digit Span Test.
- A production equivalent (research platform) that provides: O Cancellation Test, Category Fluency Test, RAVLT, COWAT and Star Cancellation.
- Paper tests: Trail Making Test, Rey Osterrieth Complex Figure Test, Digit Span Test, Controlled Oral Word Association Test, Category Fluency Test, Rey Auditory Verbal Learning Test, Clock Drawing Test, Star Cancellation Test, O Cancellation Test, MMSE-2. In addition a naming test in paper format will also be included.
- A MoCA paper based screener test.

In this study, these devices/tools will be used to investigate score distributions, construct validity and test-retest reliability.

The ISC production equivalent that will be used for administering O Cancellation Test, Category Fluency Test, RAVLT, COWAT and Star Cancellation has the exact same patient interface as the end-product. The digital tests will be provided to the participants on an iPad Pro tablet (Apple). It has a screen size of 12.9-inches with a screen resolution of 2732×2048. This is the exact same tablet as required for use of the final ISC product.

Participants will use the Apple pencil for the iPad Pro tablet to perform the digital tests (see Figure 1). The tablet will present instructions for each test to participants via both written text and audio recordings. A researcher will observe in order to ensure that the participant understands and follows the instructions (see Figure 2). The iPad Pro tablet, Apple pencil and the regular laptop, which may be used by the researcher to take notes, are all CE marked devices.

Figure 1. iPad pro and Apple pencil used by the participant

Figure 2. Regular laptop used by researcher

The ISC production equivalent and ISC product (verified for data collection, SW version 1.0.0) are only utilized to collect data. The scoring algorithms for the ROCFT and the Clock Drawing Test have either not yet been implemented or the output of those that have been implemented will not be considered relevant. The data collected with the device during the clinical investigation will be used to assess the equivalence of outputs from automatic scoring by the algorithms to traditional manual scoring. Only when the output of the algorithms have high agreement with manual scores of the respective test, the algorithms will be integrated into the final ISC product.

# 3 JUSTIFICATION

While the ISC product may be used in a variety of situations the most likely is within a neurology office. The use-case for ISC is that the raw data are collected via the ipad under the supervision of an assistant.

Subsequently, various algorithms are applied to score the individual tests. These scores are then fed into a cognitive model, resulting in easy-to-interpret cognitive domain scores. The domain scores are norm referenced by age, and optionally by gender, education, and ethnicity. The output of ISC is used by the neurologist to help him/her arrive at his/her diagnosis or for creating an optimal therapy plan. In the case of recurring visits the cognitive domain scores give the neurologist (or HCP) metrics to objectively assess change over time.

A USA neurologist will on average send 13% of his patients for a full neuropsychological assessment while in an ideal world he/she would like to send 36% (The MarkeTech Group, 2018). A common reason for not referring for a full assessment is the waiting time of 3-6 months (The MarkeTech Group, 2018). There is a clear unmet need for a solution that gives more information than a simple screener tool but within an actionable time-window, preferably during the patient vist. For the majority of patients, ISC doesn't replace the full neuropsychological assessment but instead helps triage patients so that people that need a full assessment can be quickly identified and fast tracked.

In current clinical practice, neurologists perform an MMSE or MoCA screener and occasionally a haphazard cognitive test such as a clock drawing or a simple word recall trial. In general the neurologist does not possess the skill (or time) to score tests and normative data are rarely used. Computerized cognitive assessment can alleviate issues with haphazard cognitive testing and allow more accurate cognitive assessments to be performed at the neurology office. Digitized cognitive tests have a number of important benefits compared to paper-pencil tests including norm scores at the level of cognitive domains, continuous norm scores over age, more standardized administration and scoring, dynamic presentation of the test content according to the abilities of the patient, more sensitive measurement of reaction time, additional and potentially more sensitive outcome measures, and the possibility to replay test performance (Bauer et al., 2012; Klaming & Vlaskamp, 2017; Miller & Barr, 2017; Schatz & Browndyke, 2002).

The heart of IntelliSpace Cognition is the cognitive model. The model is based on structural equation modelling, has its roots in published literature and knowledge gleaned from key opinion leaders in neuropsychology. This provided mappings between test measures and the specific cognitive domains. These mappings were fit to the data of 148 healthy individuals in an early stage pilot in the Netherlands, and showed excellent fit. Moreover, the cognitive domains specified by the model demonstrated sensitivity to impairment in 51 stroke patients and 48 TBI patients. The model is currently based on accepted test measures. In the future it may be possible to incorporate new (to be validated) outcome measures into the model and so make it more sensitive or reduce the number of tests needed. For example in current neuropsychological clinical practice, interpretation of TMT performance is mostly restricted to total completion time and errors. Other behaviours during TMT performance are likely to reveal additional information, primarily about executive functioning, but in the current paper-pencil based format of the test it is difficult or impossible to measure these behaviours. Research has already started to look into new outcome measures for the TMT that are possible with digital measurement such as inter-element variability and a separation of layout-related processes from executive processes on TMT B (Klaming & Vlaskamp, 2017). In addition, digital assessment enables more accurate measurement of total completion time and a more standardized assessment of errors during performance of the test.

Another example of a digital test is the digital administration of the ROCFT which provides a number of important benefits over paper-pencil administration. Probably most importantly, digital administration enables automatic scoring of the drawing which not only saves time in the scoring of the test, but moreover contributes to better standardization of scoring. Additionally, it will be possible to implement different scoring algorithms including both quantitative and qualitative scoring algorithms. In current neuropsychological clinical practice, formalized qualitative scoring is only rarely performed despite the fact that qualitative scoring provides additional information about the patient's cognitive functioning beyond the information provided by quantitative scoring (Akshoomoff & Stiles, 1995; Anderson, Anderson, & Garth, 2001; Bennett-Levy, 1984; Chiulli, Haaland, Larue, & Garry, 1995; Deckersbach et al., 2000; Hamby, Wilkins, & Barry, 1993; Shorr, Delis, & Massman, 1992). Besides automatic scoring which would save time and decrease variability in scoring for both qualitative and quantitative scoring systems, digital administration allows for the extraction of additional data such as touch/pencil pressure and speed which may provide additional information about the patient's cognitive functioning. The use

of computerized neuropsychological assessment has been recommended (Bauer et al., 2012; Miller & Barr, 2017; Strauss, Sherman, & Spreen, 2006).

The ISC cognitive model is based on mappings between cognitive domains and established outcome measures from well known paper-pencil tests which have many years of validation. It is vital for the validity of the digital tests, the cognitive model and their subsequent use in clinical practice that the comparibility between the digital tests on the ISC platform and the corresponding paper-pencil tests is shown. This study aims at investigating the comparibility of the relevant digital and paper-pencil cognitive tests, establishing the psychometric properties of the digital cognitive tests and collecting normative data for the digital tests so that the digital tests and the cognitive model can be used in clinical practice.Normative data is data from a reference population that establishes a baseline distribution for a score or measurement, and against which other scores or measurements can be compared. For this objective, data subjects are informed on the data we collect and the possible re-use of this data, including by 3rd parties.

# 4 RISKS AND BENEFITS ASSESSMENT

☒ I have created and uploaded a risk management summary matrix

☒ I have created and uploaded a risk management plan

A summary overview of the risks and benefits of the investigational device and the clinical procedure applied in this clinical investigation are listed in the table below.

| | |
|---|---|
| **Anticipated clinical benefits** | IntelliSpace Cognition is a digital tool to assess cognition in an efficient way. It replaces the paper workflow by a digital workflow in a healthcare facility. |
| **Anticipated adverse device effects** | There are no risks of any adverse event, mild or serious |
| **Residual risks associated with investigational device [as identified in risk analysis report]** | - No risk for participants<br><br>-Data loss (risk for validity) |
| **Risks associated with participation in clinical investigation** | - Privacy breach when devices are stolen and the system is not being logged off<br><br>- Fatigue during participation (risk is almost zero) |
| **Possible interactions with concomitant medical treatments** | There are no interactions with concomitant medical treatments |
| **Steps that will be taken to control or mitigate risks** | - Privacy breach when devices are stolen and the system is not being logged off → systems will be logged off and stored in a locked cabinet |

| | |
|---|---|
| | - Fatigue during participation → protocol will include a short break to prevent fatigue |
| **Risk-to-benefit rationale** | There are no substantial risks or potential risks possible in this trial for participants and there are no risk of any adverse event, mild or serious.<br><br>The benefits will be to be able to launch IntelliSpace Cognition and in short; speed up the cognitive access process in clinics with use of Artificial Inteligence, by replacing the paper based workflow by a digital one and it will better triage patients /subjects to which ones needs a more robust cognitive assessment with a neuropsychologist.<br><br>The benefits of the use of the investigational device outweigh the risks. |

# 5 OBJECTIVES AND HYPOTHESES

This chapter describes the objectives and hypotheses of the clinical investigation, as well as the claims and intended performance of the investigational device to be verified, and the risks and anticipated adverse device effects to be assessed.

**Primary objective:**
The study has four aims.

1. To compare the psychometrics of digital and paper-pencil cognitive tests. Score distributions, test-retest reliability, and construct validity of the following tests will be compared: Trail Making Test (TMT), Rey Osterrieth Complex Figure Test (ROCFT), Digit Span Test, Controlled Oral Word Association Test (COWAT), Category Fluency Test, Rey Auditory Verbal Learning Test (RAVLT), Clock Drawing Test, Star Cancellation Test, O Cancellation Test, Mini Mental Status Exam 2 (MMSE-2).

2. To assess the degree of agreement between the algorithm and manual scores for the digital Rey Osterrieth Complex Figure Test and Clock Drawing Test.

3. To estimate regression-based norms and reliable change indices.

4. To estimate factor loadings for a structural equation model describing cognition in terms of distinct cognitive domains.

**Secondary objective(s)**
The secondary objective of the study is to explore usability aspects of IntelliSpace Cognition.

**Primary hypotheses**
The following primary hypotheses will be tested in the study:

Aim 1.

A. Digital and paper-pencil normed test scores are comparable. We consider the two versions of a test comparable when the digital normed score is on average within .3 sd of the paper normed score and the two normed scores correlate at least .6.

B. Test-retest reliability of the digital tests is comparable to test-retest reliability of the paper-pencil tests. We consider the reliability to be comparable when we observe no significant difference in a z-test between the digital and the paper-pencil test-retest correlations.

C. Construct validity of the digital tests is comparable to the construct validity of the paper-pencil tests. We consider construct validity to be comparable when confirmatory factor analysis yields the same factor structure for digital and paper-pencil tests.

Aim 2.

D. The score(s) provided by the ROCFT and Clock Drawing Test scoring algorithms on ISC are correlated highly (> .8) to the score provided by manual scoring for the same drawings.

Aims 3 & 4 have no accompanying hypotheses.

**Secondary hypotheses**
The following secondary hypothesis will be tested in the study:

1. The usability of the ISC device is sufficient for participants or psychologists/psychometrists.

   This will be explored with a questionnaire for participants as well as a registration by the psychologist/psychometrist of how many participants were unable to complete a test and why.

**Claims and intended performance**
The study aims to provide information that can be used to substantiate the claims listed in the table below from the regulatory plan of ISC, along with the study aim covering the claim.

| Claim | Description | Covered by Study Aim |
|---|---|---|
| 1. | A scientific model developed with KOLs that translates raw test scores to cognitive domains | 4 |
| 2. | Automated scoring algorithms that give reproducible scores time after time | 2 |
| 3. | Digital tests have similar psychometrics to paper test measures | 1 |
| 4. | Longitudinal reporting of performance at the level of cognitive domains | 3 & 4 |
| 5. | Usability by Design – high "easy to use" score for elderly users | Secondary objective |
| 6. | Usability by Design - high user satisfaction when using digital platform | Secondary objective |

**Risks and adverse device effects:**
The following risks and anticipated adverse device effects to be assessed:

- Privacy breach
- Participant fatigue
- Data loss

# 6 CLINICAL INVESTIGATION DESIGN

## 6. 1 General

The study has a randomized, counterbalanced design and consists of two phases (see figure 1). We sample participants according to the sampling plan outlined below, to ensure representativeness of the sample. We will oversample by 20% to account for dropout or incomplete data (the *n*'s below represent the desired cell counts, after dropout).

**Figure 1. Schematic overview of study design.**

| Group | A | B | C | D | E |
|---|---|---|---|---|---|
| *n* | 100 | 100 | 50 | 50 | 100-150 |
| Phase 1 tests | Digital | Paper-pencil | Digital | Paper-pencil | Digital |
| Phase 2 tests | Paper-pencil | Digital | Digital | Paper-pencil | |

All participants of Group A-D in phase 1 will be invited to participate in two assessments that will take place with a time interval of four-five weeks between the two phases to minimize retest effects. Participants will be randomly assigned with minimization for demographic variables (to make sure that the groups do not differ in terms of gender, age, education level, and ethnicity) to one of the following groups:

- Group A (*n*=100) completes digital tests in phase 1 and paper-pencil tests in phase 2,
- Group B (*n*=100) completes paper-pencil tests in phase 1 and digital tests in phase 2,
- Group C (*n*=50) completes digital tests in both phases,
- Group D (*n*=50) completes paper-pencil tests in both phases,
- Group E (*n*=100-150) only completes digital tests in one phase (50% of group E will be enrolled in phase 1 and the other 50% of group E will be enrolled in phase 2).

The data of group A and B are used to compare score distributions within-subjects

The data from groups A-D (phase 1) are used to compare score distributions between-subjects (aim 1).

The data of group C and D are used to assess and compare test-retest reliability (aim 1) and assess reliable change indices (aim 3).

The data of group A (phase 1), group C (phase 1) and group E are used to estimate regression based norms for the digital tests (aim 3), as well as to estimate factor loadings for the structural equation model (aim 4).

The data of group A (phase 1), group B (phase 1), group C (phase 1) and group D (phase 1) are used to compare construct validity (aim 1).

Participants will be randomized with minimization for demographic variables (gender, age, education level, ethnicity).

The purpose of adding the 100-150 participants in Group E is to increase the sample size of participants who completed the digital tests for the first time for the norm data to 250-300.

We will use the 100 sets of digital ROCFT and Clock Drawing Test drawings, randomly drawn from the full sample, to establish agreement between scoring algorithms and manual scoring by well-trained raters (aim 2).

## 6.2 Investigational device(s) and comparator(s)

The investigational devices are the ISC product and the ISC product equivalent. The comparators are the paper-pencil tests included in the study.

Manual scores of the digital ROCFT and Clock Drawing Tests will be compared to the algorithm scores. Scoring algorithms for the ROCFT and the Clock Drawing Test are applied post-data collection. The scores estimated by the algorithms will be compared with manual scoring by a sample of well-trained raters (n = 6; aim 2). The algorithms have been developed by Philips Research and after positive comparison to the manual scores will be part of future releases of the ISC product. By comparing the manual and algorithm scoring, we can investigate the agreement between the two for the tests on the platform. This will be done by computing the relative inter-rater agreement (also known as inter-rater reliability) between the algorithm and expert raters. Relative inter-rater agreement implies that the algorithm ranks examinees the same as expert raters (n = 6).

## 6.3 Subjects

We have specified a Sampling plan that ensures representativeness for the US population in Appendix A. The sampling plan establishes initial normative reference ranges, provides psychometric evaluation of retest reliability, and provides a direct validation of digital scores relative to paper-and-pencil scores. Furthermore, this protocol establishes that older adults coming from a variety of backgrounds consistent with the general population of the United States can adequately follow the test administration rules with minimal proctoring, understand how to interact with the iPad to successfully enter his/her response to items, and a sufficient behavioral sample can be collected to establish reference ranges.

**Inclusion criteria for subject selection**

- Examinee's primary language (language most often spoken) must be English.
- If examinee has vision impairment or hearing loss, must be corrected to normal.
- Must have normal fine and gross motor ability
- Must have use of fingers, hands, and arms to be able to use a pencil to write symbols.

Must be able to understand subtest instructions and participate fully in testing

**Exclusion criteria for subject selection**

- Evidence of current cognitive impairment
- Disruptive behavior or insufficient compliance with testing to ensure a valid assessment.
- Examinee must not be currently admitted to a hospital, assisted living, nursing home or a psychiatric facility.
- Examinee must not be diagnosed with a neurological disorder or disease (e.g., Parkinson's, brain tumor, stroke, TBI, epilepsy [if # seizures ≤ 2 and not receiving ongoing treatment for seizures, and not currently seeking medical evaluation or attention related to seizures, examinee can be accepted], encephalitis, dementia, language disorder (expressive or mixed receptive/expressive excluded; articulation disorder is ok), learning disorder
- Must not have been unconscious related to traumatic brain injury or "medical condition" > 20 minutes (however, e.g., heat stroke, medication induced are ok) or any head-injury resulting in an overnight hospital stay
- Any history of a medical event requiring resuscitation in which examinee was non-responsive for > 15 minutes.
- Must not have current or recent functional change (ability to carry out usual duties at work, in school, IADLs [driving, shopping, managing money], etc.) due to cognitive change.
- Examinee must not be receiving chemotherapy treatment, or have received chemotherapy treatment in the past 2 months.
- Examinee must not have a history of ECT or radiation to the CNS.
- Examinee must not be (currently or in the past) diagnosed with a psychotic disorder, or currently diagnosed with a mood disorder (however, Major Depressive Disorder in remission or with no

current episode, and Dysthymic and Adjustment Disorders, are acceptable) or an anxiety disorder with symptoms significant enough to interfere with optimal test performance.
- Autoimmune disorder (e.g., LUPUS, Multiple Sclerosis)
- Examinee must not be currently diagnosed with substance abuse or dependence, or have carried any substance abuse or dependence diagnosis in the past year (> 1 year in remission diagnoses are ok). Long term alcohol abusers are excluded as well (e.g., abused substance for more than 10 years)
- Any history of Autism Spectrum Disorder or Intellectual Disability.
- The examinee must not be currently taking medication that might impact test performance (e.g., anti-convulsants, antipsychotics, benzodiazepines, psychostimulants, opiods, tricyclic antidepressants, some norepinephrine reuptake inhibitors). Most antihypertensive medications and statins are acceptable.
- If previously diagnosed with any physical condition or illness that might depress test performance, illness must not interfere with normal cognitive functioning at work, school, ADLs, etc. Diabetes, hypothyroidism, and hypertension are acceptable if controlled.
- Exclude primarily nonverbal or uncommunicative. Must not have a diagnosis of aphasia.
- Examinees should not have received neuropsychological testing although previous MMSE testing is allowed if more than 6 months prior
- Examinee must not be seeking medical diagnostic procedures for cognitive difficulties from a medical professional.
- Non-valid health insurance in USA.

**Criteria and procedures for subject withdrawal or discontinuation**
Subjects will be enrolled when the inclusion criteria and exclusion criteria are met and when the subject has signed the informed consent form.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

If one of the following criteria is fulfilled, the participation of a subject to the study is terminated:
- Subject indicates that he wishes to leave the study
- Subject is not able to use the iPad Pro (test data will not be destroyed but flagged as invalid)
- Subject does not meet inclusion/exclusion criteria anymore
- The investigator can decide to withdraw a subject from the study for medical reasons.

These subjects need to be replaced according to the sampling plan if test data of a subject are destroyed or test data are not complete due to study termination.

The point of enrolment is the time at which, following recruitment, a subject signs and dates the informed consent form. The first subject is expected to be enrolled in March 15 2019. The Clinical Investigation is expected to take 6 months.

The duration of each assessment is 90 minutes.

In this clinical investigation, the company that will recruit the participants will account for an expected dropout rate of 20%.

## 6.4 Procedures

**Specimen Banking (saving human fluid or tissue for future research)**

☒ Not applicable—this is a human study without specimen banking.

**Clinical procedures**
Participants included in group A-D will be invited for an assessment on two different time points (phases). Both assessments will take approximately 1.5 hours. After signing an informed consent, participants will receive either all digital or all paper-pencil cognitive tests in phase 1 and either all digital or all paper-pencil cognitive tests in phase 2, depending on group assignment. See figure 1 for

an overview of the study design. Participants included in group E of the study (see figure 1) will only receive one assessment (all digital cognitive tests). 50% of group E will be enrolled in phase 1 and the other 50% of group E will be enrolled in phase 2.
This assessment will take approximately 1.5 hours. All participants will be asked to complete a MoCA screener. The study will be concluded when each cell of the design (group A-E) meets its required sample size with participants that meet the inclusion criteria and completed the tests specified for their group.

**Sponsor activities**
Philips, as the sponsor, will be responsible for:
- Internal Ethics approval
- Providing Principal Investigator
- Study Design
- Monitoring
- Data storage
- Data integrity check
- Data analysis
- Report

**Supplier** (CRO activities):
- Selection of rooms for data collection
- Selection of psychometrists
- IRB approval
- Recruitment of participants
- Data collection

## 6.5 Monitoring plan

In accordance with 21 CFR 312.56, the clinical monitor will periodically inspect all CRFs, study documents and research facilities associated with this study at mutually convenient times during and after completion of the study. As required by FDA regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of CRFs; ensure that all protocol requirements, applicable FDA regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the investigator.. The names and identities of all research subjects will be kept in strict confidence and will not appear on CRFs or other records provided to or retained by the Sponsor. The regulations also require the investigator to allow authorized representatives of the FDA to inspect and make copies of the same records. The names and identities of the subjects need not be divulged to the Sponsor; however, the records must nevertheless be inspected. This can be accomplished by blacking out the subject's name and replacing the name with the subject's study ID number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the investigator must inform the Sponsor of these restrictions prior to initiation of the study.
See the Monitoring Plan for a description of how monitoring of the conduct and progress of the clinical study will be conducted. Monitoring of the study will be conducted by Philips according to the monitoring plan (CT18_Monitoring_Plan).

# 7 STATISTICAL CONSIDERATIONS

**Statistical design, analyses and power considerations**
Below we describe the planned analyses for each aim and hypothesis. The tests are scored by two raters (with 30% overlap) and inter-rater agreement is assessed prior to proceeding with the following analyses. All correlations mentioned below are Pearson correlations. Retest correlations are corrected for the variability of the normative sample (Allen & Yen, 2002; Magnusson, 1967). Correlation between paper and pencil measures are corrected for measurement error (Padilla & Veprinsky, 2012). In our power analyses we assume an alpha of .05.

**Aim 1 comparison of psychometrics.**

Hypothesis A: Digital and paper-pencil test scores are comparable.

For each test, we will first compute age-only referenced scores for digital and paper-pencil version separately. Referenced scores are computed based on the regression based norms (procedure described below under aim 3) and are represented as z-scores indicating a participant's deviation from what would be expected based on the norm sample for a participant with identical demographic characteristics. We then compute the correlation between digital and paper-pencil referenced scores within participants in group A and B (which are the groups in which participants completed both digital and paper-pencil versions of the tests), which needs to be $r > .6$ to be considered comparable. Our planned sample size allows us to detect a correlation of $r > .2$ with 80% power. We also perform an equivalence test for each test, comparing the distribution of digital normed scores with paper-pencil normed scores, using a two-one-sided-t-test approach (TOST; Schuirmann, 1987), with equivalence bounds of ± .3 sd, which we have 99% power to detect. Our planned sample size would allow us to detect equivalence with bounds of at least ± .21 with 80% power.

Hypothesis B: Test-retest reliability is comparable.

Test-retest reliability will be tested by examining for each test the correlation between the digital tests in phase 1 and phase 2 (group C) and comparing this to the correlation between the paper-pencil tests in phase 1 and phase 2 (group D). High test-retest correlations are expected ($r > 0.7$), except for the ROCFT copy condition, since the scores of this condition generally show a moderate ceiling effect. The planned sample size for group C and group D each yield 80% power to detect $r > .37$.

Hypothesis C: Construct validity is comparable.

Construct validity will be investigated by means of two confirmatory factor analyses (CFA), one for each group (digital vs. paper-pencil). We expect to see that the factor structure that fits the paper-pencil data (phase 1, group B & D) well, will also fit the digital data (phase 1, group A & C) well. Assuming that at most two variables per test are included in the CFA, the subject-to-variable ratio is near 10:1 for each CFA.

**Aim 2 Agreement between algorithm and manual scoring**

Hypothesis D: The score(s) provided by the ROCFT and Clock Drawing Test scoring algorithms on ISC are correlated highly (> .8) to the score provided by manual scoring for the same drawings.

For each test with algorithmic scoring, agreement with manual scoring will be tested using the two-one-sided t-tests approach (TOST; Schuirmann, 1987) on the average correlation between the algorithm and each rater on the one hand and the average correlation between the rater and each other rater on the other. Before submitting the correlations to the TOST analysis, we apply Fisher's r-to-z transformation. We will use equivalence bounds of $r \pm .1$ as a stringent criterion of practical equivalence, although we note that any correlation > .8 provides sufficient support for our claim given that the algorithms may actually be more an improvement relative to manual scoring.

We used a simulation approach to estimate the sample size of raters needed to have 80% power to detect equivalence in agreement using TOST. This approach is described in detail in Technical Note PR-TN2018/0033 (Dotsch & Klaming, 2018). For the ROCFT, the simulation approach has resulted in the recommendation that six raters will be required to score a random sample of 100 drawings from the test in order to derive at least 80% power with stringent equivalence bounds backing a strong claim of equivalence between raters and algorithm. We assumed that for the CDT a similar number of raters would be sufficient, given that scoring of drawings from both tests have generally high inter-rater agreement.

**Aim 3. Estimate regression-based norms and reliable change indices**

The data collected can be used to establish regression-based norms. 250 (up to 300) participants (group A&C, phase 1 and group E) will be included in the norm group. These norms can be used for the IntelliSpace Cognition tool and may be updated at a later point in time.

Reference scores (for age, educational level, gender, and ethnicity) will be generated using linear regression techniques. We will additionally estimate regression based reliable change indices.

**Aim 4. Estimate factor loadings for cognitive model describing**

We have developed a model of cognitive functioning using the latent variable part of structural equation modelling (which is identical to the CFA described above). We will fit the ISC model of cognitive functioning on the digital test data from Group A, C, and E, yielding a sample of 250 (up to 300) participants for the CFA, further increasing the subject-to-variable ratio to ~12:1.

**Sample size**
The study will include a total of $N$ = 400 (up to $N$=450) healthy individuals, without accounting for drop-out (see Figure 1 for the design); The tests will be scored by two well-trained raters. Moreover, to compute the inter-rater agreement between scoring algorithms and manual scoring we need six additional well-trained raters.

**Significance and power**
Please see above description.

**Expected drop-out rates**
The expected drop-out rate is 20%. The company that will recruit the participants will oversample by 20% to account for the drop-out rate, resulting in 80 additional participants recruited in addition to the 400 needed for the full design.

**Pass/fail criteria**
Please see above description.

**Interim analysis**
Not applicable.

**Termination of entire study on statistical grounds**
The study will be terminated if a sample size of $N$ = 400 with the specified distribution across age, gender, education level, and ethnicity cannot be achieved.

# 8 DATA MANAGEMENT

Data will either be captured on paper and later transcribed to the electronic case report forms (eCRFs) or directly reported into the eCRFs at the time of procedure completion. Digital test data will be captured with our digital software tools in the cloud. Ultimately, Philips will handle all data in the Datatrak system.
Researchers will be trained on the devices and the specific data management for the study prior to the start of the study. The researchers will be provided usernames and passwords unique to each researcher.
Paper source documentation (firstly documenting data on paper with later transcription into the eCRFs) shall be used for data metrics (e.g., informed consent, randomization, safety metrics captured elsewhere, eligibility metrics, standard Site forms, etc.).
Documents that may be used to capture source data on paper include, but are not limited to: standard Site forms, study diaries, or any of the Document Template forms, etc. Each paper form shall have adequate study/Site and subject identifiers and must be and remain legible. A blue or black pen should be used to document data. A pencil should never be used.

Researchers will be provided with the required forms by Philips, a paper template of the fields required to complete the eCRF. These will allow researchers to identify which data points will require documentation across the study.

**Procedures**

1. The supplier will have a compliant procedure to assure the data collection is collected according the regulations and that the data is stored and cannot be altered.
2. The data will be collected by Supplier and gathered by Philips after completion.
3. Digital data will be stored in the (Philips) cloud which is HIPAA and part 11 compliant.
4. Data will be reviewed and cleaned by Philips.
5. Philips will handle all data in the Datatrak system.

All systems that are being used are CFR part 11 compliant.

**Data retention**

Please see PIAsupport document for a detailed overview of data collected and their retention time. All records and documents pertaining to the study including, but not limited to, data and source documents, will be maintained by the sponsor for a period of 15 years. In order to avoid any possible errors, the researcher will contact the Sponsor prior to the destruction of any study records. The researchers will promptly notify the Sponsor in the event of accidental loss or destruction of any study records.

However the digital data generated by the study will be used as part of the ISC product as the ground norm data set of the device (see study objectives). These records will not be related to any patient ID, but will be delivered as part of the ISC product to future customers once the product is on the market.

**Quality Assurance**

The Sponsor or its designee will implement steps to maintain quality control (QC) and quality assurance (QA) to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, good clinical practice, and applicable regulatory requirements. This will be completed by Sponsor monitoring visits.
Regular monitoring and an independent audit, if conducted, must be performed according to ICH-GCP. QC procedures will be implemented beginning the study data QC checks will be performed. Any missing data or data anomalies will be communicated to the researchers for clarification/resolution. It is the responsibility of the researcher to respond to all edits checks and queries. Stored data as well as all data modifications to stored data will be documented by the system and available in audit trails. Following written procedures, the monitors will verify that the clinical trial is conducted and data are generated, recorded, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.
The researchers 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. In addition, post data submission, Philips (or contracted) Monitors, Project Statistician, and/or the Data Management group will remotely review data generated at different time points during the study. Data queries will be generated to resolve any discrepancies or concerns.

# 9 AMENDMENTS

Any changes to the clinical study protocol after initial ICBE approval are documented as protocol amendments. After ICBE approval, and prior to execution at the study site, the amendment will be:

- submitted and approved by the applicable IRB
- signed by the Investigator(s)

# 10 DEVIATIONS

Protocol deviations are any alteration or deviation from the ICBE-approved research plan as defined in the study protocol. This includes equipment failures during study procedures. The researcher will

deviate from the protocol whenever necessary to protect the participant's health, rights or welfare and these types of deviations will be reported to ICBE and the external IRB as soon as possible. Major deviations must be reported to ICBE and the IRB as soon as possible. In non-urgent/emergent situations, the researcher will obtain ICBE-approval for the planned deviation in advance of performing the changed activity.

If the researcher anticipates that there will be future requests for the same deviation, then the protocol will be amended (and such amendments must be approved by ICBE and the IRB). A minor deviation is something that does not cause harm or have the potential to cause harm to the participant, and does not impact the integrity of the study. These shall be documented in the study file and uploaded to ICBE for their awareness. Other reasons for amendment requests include adding a study site, increasing the number of research participants, and extending the time to perform the study. If the study objectives and procedure or cohort changes or the study changes from non-medical to medical, this generates a new study (not an amendment).

**Corrective and preventive actions and principal disqualification criteria**
When necessary, there will be given additional training to the researchers to conduct the study according to protocol.

# 11 DEVICE ACCOUNTABILITY

The procedures for the accountability of investigational devices are in accordance with the Guidance. The access to investigational devices will be controlled and the investigational devices will only be used in the clinical investigation and according to the CIP.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. This record will be based on Validation ISC – device list.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices. This is all documented in the Validation ISC – device list. This record shall include (if applicable):

- the date of receipt,
- identification of each investigational device (batch number/serial number or unique code),
- the expiry date, if applicable,
- the date or dates of use,
- subject identification,
- ate on which the investigational device was returned/explanted from subject, if applicable, and
- the date of return of unused, expired or malfunctioning investigational devices, if applicable.

# 12 STATEMENTS OF COMPLIANCE

The clinical investigation will be conducted according to the principles of the Declaration of Helsinki and other guidelines, regulations and Acts.

The clinical investigation shall not begin until the required approval/favorable opinion from ICBE and the IRB have been obtained. Any additional requirements imposed by ICBE and the IRB shall be followed.

**Compensation for injury**

General liability insurance is arranged by Royal Philips.

Sponsor wishes to obtain dispensation from statutory obligation to provide insurance, because participating in the study is without risks. A reasoned request will be made to accredited EC and this dispensation will be mentioned here.

# 13 INFORMED CONSENT PROCESS

*Select all that apply:*

☐ The requirement for informed consent has been waived (i.e., not required by law OR waived by IRB/REC/METC). Upload waiver if available.

☒ Written informed consent will be obtained from adult participants

☐ Assent will be obtained from children/minors

☐ Parental permission will be obtained when children are participating

☐ Surrogate consent will be obtained when participants lack decisional capacity

☐ Deferred consent will be obtained [e.g., emergency research]

☐ Click-through consent will be obtained [Internet/app-based research]

☐ Implied consent [i.e., consent through action such as taking a test]

13.1 Consent Process (See Section 13.3 re Assent & Permission)
Study participation is voluntary. Potential subjects, are given the most current ICBE/IRB approved consent form to read. They will be provided ample time (+1 week) for review and an opportunity to ask questions about the study. The informed consent form will be provided by the CRO during the recruitment process. If they agree to participate, the CRO will schedule the participant for participantion and they will sign the consent form before the start of the study. They will be given a copy of the signed document for their records. Each of these actions/steps will be documented. Only after Informed Consent has been obtained, may the remaining study procedures begin.

13.2 New Information about the Study
Any new information about the study that may affect a consented subject's decision to be in the study (e.g., changed procedures, safety, etc.), will be communicated in a timely manner. Depending on the nature of the new information, subjects who have completed the study may or may not be informed, documenting the decision and justification as well as any activities for informing completed subjects. Additionally, the approving IRB will also be informed. The currently approved Consent Form will be updated and submitted to the ICBE and approving IRB for review and approval. Active subjects will be re-consented, following the above process, with the newly-approved consent form.

13.3 Inability to Provide Consent (children or adults)
N/A

# 14 ADVERSE EVENTS AND DEVICE DEFICIENCIES

**Definitions**

Adverse events and adverse device effects, device deficiencies and serious adverse events and serious adverse effects and, unanticipated serious adverse device effects are defined in the table below:

| *Definition* | *Description* |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device<br>NOTE 1 This definition includes events related to the investigational medical device or the comparator.<br>NOTE 2 This definition includes events related to the procedures involved.<br>NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices. |
| Adverse Device Effect (ADE) | Adverse event related to the use of an investigational medical device<br>NOTE 1 This definition includes events related to the investigational medical device or the comparator.<br>NOTE 2 This definition includes events related to the procedures involved.<br>NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices. |
| Serious Adverse Event (SAE) | Adverse event that<br>a) led to death,<br>b) led to serious deterioration in the health of the subject, that either resulted in<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, or<br>3) in-patient or prolonged hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) led to foetal distress, foetal death or a congenital abnormality or birth defect<br>NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious<br>deterioration in health, is not considered a serious adverse event. |
| Serious Adverse Device Effect (SADE) | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less |
| Unanticipated Adverse Device Effect (UADE) | Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report<br>NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. |

**Reportability**
All adverse events shall be reported to the Study Manager. ADEs, SAEs, SADEs and USADEs shall be reported to the Q&R office as well. The Director Q&R shall assess the ADEs, SAEs, SADEs and USADEs for reportability to Competent Authorities.

**Reporting process**
Reporting shall include the date of the adverse event, research subject ID#, description of the adverse event, treatment, resolution, and assessment of both the seriousness and the relationship to the investigational device and study procedures.

**Timelines**
The time period in which the principal investigator shall report all adverse events and device deficiencies to the sponsor and, where appropriate, to ECs and the regulatory authority, and the details of the process for reporting device deficiencies, are detailed in the table below.

<table>
<tr><td>Category</td><td>Report to Study Manager</td><td>Report to Accredited Ethics Committee</td><td>Report to Q&R office</td></tr>
<tr><td></td><td>by<br>Principal Investigator</td><td>by<br>Principal Investigator</td><td>by<br>Principal Investigator<br>by Study Manager</td></tr>
<tr><td>Adverse Event (AE)</td><td colspan="3">Periodic reporting to Sponsor<br>Periodic collection by Sponsor<br>As part of Sponsor's Clinical Investigation Report</td></tr>
<tr><td>Adverse Device Effect (ADE)</td><td rowspan="4">Immediate, < 24 hr</td><td>As part of Ethics Committee Reporting timelines<br>or<br>< 24 hr following instructions by Sponsor</td><td rowspan="4">Immediate, <24 hr</td></tr>
<tr><td>Serious Adverse Event (SAE)</td><td>As part of Ethics Committee Reporting timelines<br>or<br>< 24 hr following instructions by Sponsor</td></tr>
<tr><td>Serious Adverse Device Effect (SADE)</td><td>Immediate, < 48 hrs</td></tr>
<tr><td>Unanticipated Adverse Device Effect (UADE)</td><td>As part of Ethics Committee Reporting timelines<br>or<br>< 24 hr following instructions by Sponsor</td></tr>
</table>

**Foreseeable adverse events and anticipated adverse device effects**
No adverse events and anticipated adverse device effects are foreseen. The only event we foresee is fatigue of participants that are participating in our study.
Since there are no possible adverse events, there is no foreseen need to contact the IRB .
Device malfunction will be reported to the sponsor directly who then needs to take a decision to stop/suspend or continue the trial depending the software fault and the risks of achieving the trial objectives. There is no risk for the subjects even if the device is at fault.

**Emergency contact details**
N/A

**Information regarding the Data Management Committee, if established**
N/A

**Incidental Finding Reporting**
An Incidental Finding is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study.

All incidental findings will be documented in a timely manner throughout the study. The report Incidental Finding Report Form (see ICBE SP) will be in the receipt of Philips Research Q&R Office within 7 business days of when the researcher first learns about the finding.

## 15 INVESTIGATOR BROCHURE (IB)

An IB is needed and included in the ICBE study dossier.

## 16 VULNERABLE POPULATION

According to ISO 14155, a vulnerable subject is an individual whose willingness to volunteer in a clinical study could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

☐ None—this study uses live human participants but not from vulnerable populations

*Indicate whether you will include any of the following (vulnerable) populations in your study:*

☐ Children or viable neonate (birth to age 28 days)

☐ Cognitively impaired

☐ Pregnant women (except USA)

☐ Fetuses

☐ Neonates of uncertain viability or nonviable

☐ Prisoners

☐ Poor/uninsured

☒ Educationally disadvantaged (limited education, e.g., high school drop out)

☐ Students (including interns, residents, fellows)

☐ Minorities (includes migrants, refugees)

☒ Elderly (over age 65 years)

☐ Terminally ill

☐ Other (check box and specifically discuss below)

*Informed consent form will be provided with detailed information about the study. Psychometrists who are experienced with this age group will collect the data.*

## 17 SUSPENSION OR PREMATURE TERMINATION

In case the study is ended prematurely, the investigator will notify the IRB and the ICBE about the reasons for the premature termination.

The principal investigator or authorized designee shall inform the subjects of the reasons for resumption.

The following criteria and arrangements for suspension or premature termination of the whole clinical investigation or of the clinical investigation in one or more investigation sites apply:

- Philips decides to stop the study.

In case of suspension or premature termination of the clinical investigation, the following requirements apply for subject follow-up.

- N/A

## 18 PUBLICATION POLICY

Results of clinical investigation may be submitted for publication. Philips shall register and report the results of this applicable trial on clinicaltrials.gov.

## 19 BIBLIOGRAPHY

List of bibliographic references pertaining to clinical investigation

Allen, M. J., & Yen, W. M. (2002). Introduction to measurement theory. Long Grove, IL: Waveland Press.

Akshoomoff, N. A., & Stiles, J. (1995). Developmental trends in visuospatial analysis and planning: memory for a complex figure. *Neuropsychology, 9(3)*, 378-389.

Anderson, P., Anderson, V., & Garth, J. (2001). Assessment and development of organizational ability: the Rey Complex Figure Organizational Strategy Score (RCF-OSS). *The Clinical Neuropsychologist, 15(1)*, 81-94.

Bauer, R.M., Iverson, G.L., Cernich, A.N., Binder, L.M., Ruff, R.M., & Naugle, R.I. (2012). Computerized neuropsychological assessment devices: joint position paper of the American Academy of Clinical Neuropsychology and the National Academy of Neuropsychology. *Archives of Clinical Neuropsychology, 27*, 362-373.

Bennett-Levy, J. (1984). Determinants of performance on the Rey-Osterrieth Complex Figure Test: an analysis, and a new technique for single-case assessment. *The British Journal of Clinical Psychology / the British Psychological Society, 23 (Pt 2)*, 109-119.

Chiulli, S. J., Haaland, K. Y., Larue, A., & Garry, P. J. (1995). Impact of age on drawing the Rey-Osterrieth figure. *The Clinical Neuropsychologist, 9(3)*, 219-224.

Deckersbach, T., Savage, C. R., Henin, A., Mataix-Cols, D., Otto, M. W., Wilhelm, S., ... Jenike, M. A. (2000). Reliability and validity of a scoring system for measuring organizational approach in the Complex Figure Test. *Journal of Clinical and Experimental Neuropsychology, 22(5)*, 640-648.

Fortuny, L.A., & Heaton, R.K. (1996). Standard versus computerized administration of the Wisconsin Card Sorting Test. *The Clinical Neuropsychologist, 10(4)*, 419-424.

Greve, K.W. (1993). Can perseverative responses on the Wisconsin Card Sorting Test be scored accurately? *Archives of Clinical Neuropsychology, 8*, 511-517.

Hamby, S. L., Wilkins, J. W., & Barry, N. S. (1993). Organizational quality on the Rey-Osterrieth and Taylor Complex Figure Tests: a new scoring system. *Psychological Assessment, 5(1)*, 27-33.

Klaming, L., & Vlaskamp, B.N.S. (2017). Non-dominant hand use increases completion time on part B of the Trail Making Test but not on part A. *Behavior Research Methods*, 1-14.

Magnusson, D. (1967). Test theory. Reading, MA: Addison-Wesley.

The MarkeTech group (2018). An online survey of 75 US-based neurologists, conducted by The MarkeTech Group.

Miller, J.B., & Barr, W.B. (2017). The technology crisis in neuropsychology. *Archives of Clinical Neuropsychology*, 1-14.

Padilla, M. A., & Veprinsky, A. (2012). Correlation Attenuation Due to Measurement Error: A New Approach Using the Bootstrap Procedure. *Educational and Psychological Measurement*, *72*(5), 827–846. https://doi.org/10.1177/0013164412443963

Paolo, A.M., Axelrod, B.N., & Ryan, J.J. (1994). Administration accuracy of the Wisconsin Card Sorting Test. *The Clinical Neuropsychologist, 8(1)*, 112-116.

Schatz, P., & Browndyke, J. (2002). Applications of computer-based neuropsychological assessment. The *Journal of Head Trauma Rehabilitation, 17(5)*, 395-410.

Shorr, J., Delis, D., & Massman, P. (1992). Memory for the Rey-Osterrieth Figure: perceptual clustering, encoding, and storage. *Neuropsychology, 6*, 43-50.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A compendium of neuropsychological tests: administration, norms, and commentary* (3rd ed.). New York: Oxford University Press.

Tien, A.Y, Spevack, T.V., Jones, D.W., Pearlson, G.D., Schlaepfer, T.E., & Strauss, M.E. (1996). Computerized Wisconsin Card Sorting Test: comparison with manual administration. *Kaohsiung Journal of Medical Sciences, 12*, 479-485.

An online survey of 75 US-based neurologists, conducted by MarkTech Group, revealed that the average waiting time for a neuropsychological evaluation is 7.6 weeks.

5 75 US-based neurologists were asked; "For what percentage of all your patients do you currently request a full neuropsychological assessment?" The average of all responses was 13%. They were then asked, "In an ideal world which percentage of all your patients would you like to send for a full neuropsychological assessment?" The average of all responses was 36%.

[End of document]

**Fully Crossed Targets**

| | | Male | | | | | | | | | | | | Female | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | White | | | Black | | | Hispanic | | | Other | | | White | | | Black | | | Hispanic | | | Other | | |
| | Years of eduction | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years | < 12 years | 12 years | > 12 years |
| Age range | | | | | | | | | | | | | | | | | | | | | | | | | |
| 50-54 | 50 | 1 | 5 | 10 | 1 | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 2 | 1 | 5 | 11 | 0 | 1 | 2 | 1 | 1 | 2 | 0 | 0 | 1 |
| 55-59 | 50 | 1 | 5 | 11 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 6 | 11 | 0 | 1 | 2 | 1 | 1 | 1 | 0 | 0 | 1 |
| 60-64 | 50 | 1 | 4 | 12 | 1 | 2 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 6 | 12 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 |
| 65-69 | 50 | 1 | 5 | 12 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 6 | 12 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 |
| 70-74 | 50 | 1 | 5 | 12 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 7 | 11 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 |
| 75-80 | 50 | 2 | 6 | 11 | 1 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 1 | 3 | 8 | 10 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |

**Marginals Target**

| | | Male | female | White | Black | Hispanic | Other | < 12 years | 12 years | > 12 years |
|---|---|---|---|---|---|---|---|---|---|---|
| 50-54 | 50 | 25 | 25 | 33 | 7 | 7 | 3 | 5 | 15 | 30 |
| 55-59 | 50 | 25 | 25 | 35 | 6 | 6 | 3 | 5 | 16 | 29 |
| 60-64 | 50 | 25 | 25 | 36 | 6 | 5 | 3 | 5 | 16 | 29 |
| 65-69 | 50 | 25 | 25 | 37 | 5 | 5 | 3 | 5 | 15 | 30 |
| 70-74 | 50 | 25 | 25 | 37 | 6 | 5 | 2 | 6 | 15 | 29 |
| 75-80 | 50 | 25 | 25 | 40 | 4 | 4 | 2 | 9 | 18 | 23 |

**Variance Matrix**

| | | Age Variance | Male | female | Sex Variance | White | White Variance | Black | Black variance | Hispanic | Hispanic Variance | Other | Other Variance | < 12 years | < 12 Variance | 12 years | 12 Variance | > 12 years | 12 Variance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 50-54 | 50 | 1 | 25 | 25 | ± 2 | 33 | -1 | 7 | ± 1 | 7 | ± 1 | 3 | at least 2 | 5 | exact | 15 | ± 1 | 30 | ± 2 |
| 55-59 | 50 | 1 | 25 | 25 | ± 2 | 35 | -1 | 6 | ± 1 | 6 | ± 1 | 3 | at least 2 | 5 | exact | 16 | ± 1 | 29 | ± 2 |
| 60-64 | 50 | 1 | 25 | 25 | ± 2 | 36 | -1 | 6 | ± 1 | 5 | ± 1 | 3 | at least 2 | 5 | exact | 16 | ± 1 | 29 | ± 2 |
| 65-69 | 50 | 1 | 25 | 25 | ± 3 | 37 | -1 | 5 | ± 1 | 5 | ± 1 | 3 | at least 2 | 5 | exact | 15 | ± 1 | 30 | ± 2 |
| 70-74 | 50 | 1 | 25 | 25 | ± 3 | 37 | -1 | 6 | ± 1 | 5 | ± 1 | 2 | at least 1 | 6 | exact | 15 | ± 1 | 29 | ± 2 |
| 75-80 | 50 | 1 | 25 | 25 | ± 3 | 40 | -1 | 4 | ± 1 | 4 | ± 1 | 2 | at least 1 | 9 | exact | 18 | ± 1 | 23 | ± 1 |
| total | 250 | 250 | at least 115 | No more than 135 | ± 10 | 185 | up to -5 | 27 | at least 25 | 25 | at least 22 | 13 | at least 8 | 30 | at least 30 | 80 | at least 75 | 140 | at least 130 |