1. Original data could be submitted in Excel file format if determined to be necessary by the editors and reviewers.
2. University of Rochester Research Subjects Review Board approved protocol and consent form below:

Evaluation of Cognition in Patients with Multiple Sclerosis Using Cognivue®

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1. PURPOSE OF THE STUDY AND BACKGROUND

1.1. Purpose of the study

The purpose of the study is to pilot a novel computer-based cognitive testing, Cognivue®, in patients with multiple sclerosis. Cognivue® recently gained FDA approval for monitoring of early signs of dementia, but has not been used to study cognition in patients with multiple sclerosis. Secondary areas of investigation will include comparing cognitive performance between patients with Multiple Sclerosis and age-matched controls, comparing testing results between Cognivue and validated cognitive tests in the MS population (Symbol Digit Modalities Testing). Below are the project’s hypotheses.

1) Cognivue® will be able to at least detect cognitive deficits that are detected in current standard testing in patients with MS, i.e. Symbol Digit Modalities Test and Paced Auditory Serial Addition Test.
2) Cognivue will have excellent test-retest reliability in both patients and controls.
3) Patients with MS will have more cognitive deficits than age matched controls.

1.2 Background

It is well known that multiple sclerosis has a deleterious effect on cognition. While MS was once thought to be principally due to demyelination, it is now well recognized that diffuse grey-matter atrophy also occurs. The combination of these two pathological processes, while not completely understood at this time, leads to heterogeneous cognitive dysfunction in many patients with both relapsing and progressive MS (1, 2).
Several clinical tests have been designed for rapid, objective testing including paced auditory serial addition test (PASAT) and the symbol digit modalities test (SDMT) \(^{(3, 4)}\). While these tests have high inter-rater and test-test reliability they primarily test subcortical cognitive processes and ability to assess speed of processing. Given what we know of MS to date, that it is both a white matter and grey matter disease, this information may have significant relevance in determining disease activity/progression, assessing benefits of symptomatic treatment of cognitive function, and understanding functional limitations.

Recently, the Cognivue\textsuperscript{®} computer-monitor based testing has been shown to be effective tool in determining cognitive dysfunction in patients with Alzheimer’s disease \(^{(5)}\). This testing modality uses patient guided joystick movements for subject choice-making in letter discrimination, word discrimination, visual motion discrimination, and short-term recall in each of these facets. The test yields rich, reproducible data that highly correlates with mini-mental status examination. Additionally, this testing is highly reliant on intact cortical and subcortical functioning that we hypothesize makes it a promising candidate for testing in patients with multiple sclerosis.

Both the PASAT and SDMT are relatively easy to administer and take no more than 15 minutes. However, neuropsychological testing which and further evaluate cortical function can take over 1 hour to administer. This can certainly be a burden to both the patient and the examiner. It also makes assessment of cortical function in the day-to-day clinical setting impractical. On the other hand, Cognivue\textsuperscript{®} can be completed in 10 minutes and does not require any additional time of the clinician to administer a test or complete further training.

This computer-monitor based testing may have significant importance to understanding cognitive dysfunction in patients with multiple sclerosis. First, it will likely result in rich individual-specific functional data that can be easily tracked over time. Secondly, it may give more insight into the role of white matter and cortical pathology in patients with MS. And lastly, based on experience in Alzheimer disease, it can be easily used in the routine clinical setting and has the potential for uses as an outcome measure for cognition in RCTs.

2. STUDY DESIGN

2.1. Overview

The study will be a single center multiple time point assessment of cognition using the Cognivue\textsuperscript{®} system in patients with multiple sclerosis. Control testing will include the Paced Auditory Serial Addition Test (PASAT) and 9-hole peg test (As well as further components of
the MS function composite including a time 25 foot walk and expanded disability status scale). Following baseline testing each MS and control participant will undergo Cognivue® testing on a monthly basis for a total of 3 assessments.

Cognivue® engages patients in continuous stimulus-response paradigms that demand an intervening cognitive process. This is accomplished by recording the patient’s ability to respond to a battery of ten tests that present variations of visual stimuli. In all ten tests, the subject tracks the movement of a cursor-width target wedge (pie slice), or responds to visual tasks presented in an annular display by using a rotatory manipulandum wheel to control and place the green cursor over the target wedge or other appropriate response.

The testing begins with basic visual and motor testing (ability to perceive the visual stimuli and move the manipulandum) which standardizes the rest of the cognitive testing to the patient's visual and motor abilities. The Cognivue® screening battery proceeds with four perceptual processing tests of letter, word, shape, and motion processing. Each test category is presented in a series of parametric variants that test the vulnerability of processing to confounding influences that are related to the mechanisms of brain processing in the targeted domain. Following each perceptual task a recall/short-term memory task in the same field is conducted. All testing, reporting, and record keeping are conducted in a manner consistent with relevant regulatory guidance for the protection of patient confidentiality.

2.2. Rationale for Study Design

The rationale for the study design is several fold. 1) We will be able to compare established cognitive test in patients with MS (PASAT and SDMT) with Cognivue®. 2) We will be able to explore Cognivue® test-test variability in patients with MS as well as healthy controls within the same age range. The use of one to two month intervals of testing was pragmatically determined to be more feasible for the study population than 1 week or quarterly. Additionally, the shorter the interval the more likely the testing is to be stable.

Additionally, we will include the Multiple Sclerosis Functional Composite (MSFC). The MSFC includes PASAT, 9-hole peg test, and timed 25 foot walk. This is a well established composite measure that has been validated in in a variety of MS populations including in randomized, control clinical trials. We will also obtain a baseline The Kurtzke Expanded Disability Status Scale (EDSS) which is an established standardized scoring examination that places a larger emphasis on ambulation (which has a close association with disease severity and disability). Neither the MSFC or EDSS will be used as a screening tool for subject selection/enrollment.
3. CHARACTERISTICS OF THE RESEARCH POPULATION

3.1. Subject Characteristics

a) Number of Subjects:

We plan on enrolling a total of 60 subjects: 30 patients with MS and 30 controls. Discussion on rationale for subject population is found in section 12.1.

b) Gender and Age of Subjects:

Subjects and controls will be between the ages of 18-50 years. The upper limit of 50 years is to avoid cognitive impairment that could be attributed to known changes in cognition with maturity.

There will be no preference in regards to sex in the enrollment although we anticipate a higher proportion of females due to the known epidemiology.

c) Racial and Ethnic Origin: MS is less prevalent in African-Americans and rare in Asian-Americans. Although every effort will be made to be inclusive during recruitment, we anticipate that enrollment will reflect these known epidemiological features of MS.

d) Vulnerable Subjects: N/A

3.2. Inclusion and Exclusion Criteria

- Inclusion Criteria:
  
  Subject Inclusion Criteria
  
  - Clinically diagnosed MS based on 2010 Revised MacDonald Criteria
  - Age 18 - 50

Control Population Inclusion Criteria

  - Age 18 - 50

- Exclusion Criteria

Subject Exclusion Criteria:

  - Radiological or clinical MS exacerbation 3 months prior to enrollment or during study period
  - Unable to read or sign consent or lack capacity for consent
  - Depression (Hamilton Questionnaire) > 20 *
  - History of cognitive impairment attributable to another cause

Control Population Exclusion Criteria
3.3. **Discussion of Subject Population**

Subject population selection criteria were made to identify patients in a static clinical status in regards to cognitive function. Further enrollment criteria, including age, depression, and history of cognitive impairment related to another cause are applied in attempt to exclude confounding causes of cognitive impairment. Inability to read or sign the consent form was used in prior research protocols of Cognivue®, as these impairments would likely lead to inability to ascertain the visual cues on the monitor and operate the rotatory manipulandum wheel. The Cognivue® has the ability to handicap visual and motor impairment of the dominant hand such that it may not significantly affect the results of cognitive testing.

4. **SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT**

4.1. **Method Of Subject Identification And Recruitment**

Treating physicians within the University of Rochester Department of Neurology will identify potential subjects. Following identification of a possible subject, the treating physician will contact the principal investigator (PI). The PI will review the research protocol and consent form with the subject and together will attempt to identify an age-matched control that will volunteer (spouse, friend, or relative) to enroll as an age-matched control. After obtaining consent the subject and control for participation of the study a schedule will be agreed upon for baseline testing and repeat Cognivue®, SDMT and PASAT testing. A subject will be identified by a unique 4 digit identifier. The examiner will not be blinded to subject and control. The Cognivue® computer is able to store personal identifiers, but when data is transferred from the computer to a USB portable storage drive the simple 4 digit ID number will be used to identify each subject and control (e.g., 1001, 1002, etc).

This data will then be transferred to a URMC IT security compliant computer for data analysis. Data collected at the first visit will be obtained from the patient and confirmed with the
treating physician. The consent process will include allowing the research physicians access to the subjects medical record for review.

Control subjects will be recruited primarily through recommendation of the MS subject. The same inclusion and exclusion criteria will apply. In cases were there is no identifiable or willing volunteer with relation to the subject, participants will be recruited from within the medical community. In either case, the researchers will not pursue access to their medical records. If a member of the medical staff is recruited into the study it will be clear that agreement/decline to participation will not affect their employment.

4.2. Process of Consent

The PI will obtain informed consent (both patients with MS or control). This will likely occur most frequently while the patient is being evaluated in the URMC Neurology Clinic (AC-1). The PI meets with the patient and confirms inclusion and exclusion criteria as well as discusses the study protocol and consent form. It will be clear to the subjects that there will be no reimbursement and that participation will not have any influence on their ongoing medical treatment (applicable for MS patients). If a patient is not ready to enroll and would like to contemplate enrollment, the investigator will discuss method of follow-up communication to discuss enrollment.

Consent will be obtained on paper and stored securely in the URMC Neuroimmunology administrative office. Storage will be in compliance with the RSRB requirements.

2) Subjects who previously had consented to testing once per month under the previous protocol, will be notified of liberalization of testing to once every 30-60 days through a letter (Appendix 5) that will either be given to them in person at their next study visit.

5. METHODS AND STUDY PROCEDURES (see Appendix 1 for study schedule)

All study activities will occur in the University of Rochester Medical Center, Ambulatory Center, Neurologic Clinic on the 1st floor or in the Cognitive and Aging Laboratory (3.5704) in the Eastman School of Medicine and Dentistry. One Cognivue system will be stored in the shared, secure (door has card swipe access), clean utility room on the 1st floor. The second Cognivue system will be stored in the Cognitive and Aging Laboratory (3.5704). The computer station has clear identification of operators of the device including the PIs Name, e-mail address. It also has contact information for the manufacturing company, Cerebral Assessment Systems. Login access will be restricted to investigation team.

Enrollment Visit: Consent, Collection of baseline data, Agreement on Schedule of testing visits
Baseline data will include:

- evaluation of inclusion/exclusion criteria including Hamilton Depression Rating Scale (Appendix 2)
- Perceived Deficits Questionnaire - 5 Item (Appendix 3)
- Current disease modifying therapy
- Symptomatic treatment: amantadine, amphetamines, choline estersterase inhibitors
- Time since diagnosis, # clinical or radiological exacerbations in the last 6mo

5.1. Safety Assessments: N/A

5.2. Assessment of Subject Compliance

If the subject is only able to complete one or two examinations, their data will be included. However, notation of lack of completion of the study will be made and used for qualitative analysis of feasibility of testing.

5.3. Data & Specimen Banking for Future Research Use:
Data will be stored for a period of approximately 2 years. Data will be stored as per URMC guidelines (see section 10).

5.4. Costs to the Subject
There will be no direct costs associated with testing.

5.5. Payment for Participation
There will be no reimbursements for subject or control participation.

5.6. Return of Individual Research Results
The results of testing will not be available to the participants.

5.7. Payment for Participation
Subjects will be reimbursed for their participation in the study. The reimbursement will be $20 dollars per study visit which will be dispersed upon their completion in the study. If a patient withdraws from the study prior to completion of the study they will be reimbursed for the number of study visits in which they participated. Documentation of participating in study activities will be recorded in a separate Excel file to track participation for remuneration. Once a subject has completed all study activities or is no longer eligible to continue with study activities (unable to attended the next study visit due to interval time constraints) the University of Rochester Department of Neurology Research Administrators will be notified and a request for payment to Accounts Payable will then cut a check using funds from a research award granted by the Department of Neurology to the PI to be sent to the subject.

6. CONCOMITANT AND DISALLOWED MEDICATIONS
None

7. SUBJECT WITHDRAWALS
Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice. If subjects are unable to complete the study they will be withdrawn. If a medical staff member withdraws there will be no repercussions to this decision.

8. SAFETY AND REPORTABLE EVENTS

There are no anticipated serious events associated with testing.

9. RISK/BENEFIT ASSESSMENT

9.1. Potential Risks

Potential risks of participation include stress of testing as well as possible physical stress or discomfort from maneuvering the joystick, 9-hole peg test. It is also possible that despite efforts elaborated in this protocol (outlined in Section 10) that confidentiality may be lost. If this were to occur it would be reported to the RSRB as well as communicated to the subject.

9.2. Protection Against Risks

If the patient develops fatigue or discomfort during testing, a break in testing will be allowed before returning to testing. If the patient is not able to participate in the study on a scheduled testing time, the subject may reschedule.

If the subject has worsening or exacerbation of disease during the study the patient will be withdrawn from the study. This will be determined in discussion with the patient, the treating physician and the study investigator.

9.3. Potential Benefits to Subjects

There are no known direct benefits to subjects anticipated.

9.4. Alternatives to Participation

The subject does not have to participate in this study.

10. CONFIDENTIALITY OF DATA AND INFORMATION STORAGE

On the completion of Cognivue testing, the system combines 1) identifying information on the tested patient, 2) the raw response waveforms obtained in testing, and 3) the derived results of those tests. Those data are then combined with the specifics of the date, time, and location of testing as well as sufficient specification of the tests performed.

This information is archived on the test system, re-formatted and entered into the established database. The results of any previous testing of that patient are integrated into the data display as a separate time-based line plot with specific labeling. These format data displays are then converted into a portable document file. The document file can be printed at the test site for the immediate review by the responsible healthcare professional. Alternatively or additionally, the report document can be transferred electronically. All data storage and transfer is executed with the highest regards to health information protection in compliance with relevant regulatory guidance (HIPAA, etc.).

11. RESEARCH INFORMATION IN MEDICAL RECORDS
No research data will be included in the subject’s medical record.

12. DATA ANALYSIS AND MONITORING
12.1. Sample Size Determination

A sample size of 30 MS subjects will provide > 80% power to detect that an intra-class correlation coefficient for test-retest reliability is significantly greater than a null hypothesis value of 0.70 (minimum acceptable) when the true value is 0.85 or higher, using a one-tailed test with a 5% significance level.

Sample sizes of 30 MS subjects and 30 healthy controls will provide > 80% power to detect a difference in mean response of 0.75 standard deviation units between the MS and control groups with respect to cognitive test scores, using a t-test and a 5% significance level (two-tailed). An effect size of this magnitude, while fairly large, is nevertheless expected based on a prior study by Parmenter et al using the Symbols Digit Modalities Test which showed a greater than 1 SD difference between patients with MS and healthy controls. Additionally, in a prior study using Cognivue composite memory scores the means were 88.2 and 77.8 with respective standard deviations of 17.0 and 8.3 for unimpaired and mildly impaired subjects respectively (data obtained from Dr. Duffy). Therefore, it is reasonable to hypothesize that the difference in Cognivue scoring means in patients with MS and controls may be greater than 1 SD.

12.2. Planned Statistical Analysis

Primary analyses:
- Participant study completion
- Test-retest reliability Cognivue® total score and subset scores
- Test-retest reliability in SDMT and PASAT scores

Secondary analyses:
- Comparison of MS and healthy volunteers Cognivue® scores
- Correlation between subjective cognitive dysfunction and Cognivue® or PASAT scores

Analysis of study completion will be purely descriptive, with summaries of the percentage of subjects who complete 1, 2, and all 3 study visits.

Intra-class correlation coefficients will be used to quantify the reliability of the Cognivue total and subscale scores and the SDMT and PASAT scores. These will be derived from two-way mixed effects models including a random effect for subject and a fixed effect for visit. Bland-Altman plots will also be used for graphical examination of reliability. Separate analyses will be performed for MS subjects and healthy controls.

Composite Cognivue, SDMT and PASAT scores in subjects with multiple sclerosis and healthy controls will be compared using either t-tests or Wilcoxon rank sum tests depending on whether the data appear to be normally distributed. Data from the first subject visit will be used for these analyses.

Pearson correlations (or Spearman rank correlations, if appropriate) will be computed among Cognivue scores, SDMT scores, PASAT scores, and the Perceived Deficits Questionnaire total score. Also, individual scores for the Cognivue, SDMT and PASAT tests will be compared to established cut-offs...
for cognitive impairment in each test. Classifications of normal/abnormal performance will be cross-tabulated between these three testing modalities. Again, data from the first subject visit will be used for these analyses.

12.3. **Data and Safety Monitoring**

The PI will monitor collection, storage, and processing of data. This will proceed as indicated above. If there are any changes in protocol of collection, storage, and processing of data this will be presented to the RSRB for approval. If there are any errors in handling of collected data this will be urgently reported to the RSRB.

The type of study does not warrant further monitoring (i.e., DSMB).

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Appendix 1

Schedule of Activities

| Visit                    | 0 (Screening) | 1 | 2 | 3          |
|--------------------------|---------------|---|---|------------|
| Visit Window             | -30 to -60 days | 0 days | 30-60 days later | 30-60 days later |
| Obtain informed consent  | X             | (X) |   |            |
| Confirm eligibility/Enroll|               | X  |   |            |
| Medical history and demographics | X   |     |   |            |
| MSQOL: Perceived Deficits Questionnaire - 5 item | X |     |   |            |
| Hamilton Depression Scale Inventory | X |     |   |            |
| Multiple Sclerosis Functional Composite | X | | | |
| Kurtzke Expanded Disability Scale | X |  | | |
| Cognivue® | X | | | |
| Paced Auditory Serial Addition Test | X | X | | |
| Symbol Digit Modalities Test | X | X | | |

Appendix 2

Hamilton Depression Rating Scale

DEPRESSED MOOD

(sadness, hopeless, helpless, worthless)

0 |__| Absent.

1 |__| These feeling states indicated only on questioning.

2 |__| These feeling states spontaneously reported verbally.

3 |__| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.

4 |__| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT

0 |__| Absent.

1 |__| Self reproach, feels he/she has let people down.
2 |___| Ideas of guilt or rumination over past errors or sinful deeds.
3 |___| Present illness is a punishment. Delusions of guilt.
4 |___| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

**Hamilton Depression Rating Scale (HDRS)**

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one “cue” which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

**3 SUICIDE**

0 |___| Absent.
1 |___| Feels life is not worth living.
2 |___| Wishes he/she were dead or any thoughts of possible death to self.
3 |___| Ideas or gestures of suicide.
4 |___| Attempts at suicide (any serious attempt rate 4).

**4 INSOMNIA: EARLY IN THE NIGHT**

0 |___| No difficulty falling asleep.
1 |___| Complains of occasional difficulty falling asleep, i.e. more than 1/2 hour.
2 |___| Complains of nightly difficulty falling asleep.

**5 INSOMNIA: MIDDLE OF THE NIGHT**

0 |___| No difficulty.
1 |___| Patient complains of being restless and disturbed during the night.
2 |___| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

**6 INSOMNIA: EARLY HOURS OF THE MORNING**

0 |___| No difficulty.
1 | __ | Waking in early hours of the morning but goes back to sleep.

2 | __ | Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES

0 | __ | No difficulty.

1 | __ | Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.

2 | __ | Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).

3 | __ | Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.

4 | __ | Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION

(slowness of thought and speech, impaired ability to concentrate, decreased motor activity)

0 | __ | Normal speech and thought.

1 | __ | Slight retardation during the interview.

2 | __ | Obvious retardation during the interview.

3 | __ | Interview difficult.

4 | __ | Complete stupor.

9 AGITATION

0 | __ | None.

1 | __ | Fidgetiness.

2 | __ | Playing with hands, hair, etc.

3 | __ | Moving about, can’t sit still.

4 | __ | Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC

0 | __ | No difficulty.

1 | __ | Subjective tension and irritability.

2 | __ | Worrying about minor matters.
3 | ___ | Apprehensive attitude apparent in face or speech.
4 | ___ | Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:
gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating
0 | ___ | Absent.
1 | ___ | Mild.
2 | ___ | Moderate.
3 | ___ | Severe.
4 | ___ | Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL
0 | ___ | None.
1 | ___ | Loss of appetite but eating without encouragement. Heavy feelings in abdomen.
2 | ___ | Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS
0 | ___ | None.
1 | ___ | Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 | ___ | Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)
0 | ___ | Absent.
1 | ___ | Mild.
2 | ___ | Severe.
### 15 HYPOCHONDRIASIS

|   |   | Not present. |   |   |
|---|---|--------------|---|---|
| 0 |   | Self-absorption (bodily). |   |   |
| 1 |   | Preoccupation with health. |
| 2 |   | Frequent complaints, requests for help, etc. |
| 3 |   | Hypochondriacal delusions. |

### 16 LOSS OF WEIGHT

**RATE EITHER a OR b**

|   |   | No weight loss. |   |   |
|---|---|----------------|---|---|
| 0 |   | Less than 1 lb. weight loss in week. |
| 1 |   | Probable weight loss associated with present illness. |
| 2 |   | Greater than 1 lb. weight loss in week. |
| 3 |   | Greater than 2 lb. weight loss associated with present illness. |

### 17 INSIGHT

|   |   | Acknowledges being depressed and ill. |
|---|---|---|
| 0 |   | Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. |
| 1 |   | Denies being ill at all. |

Total score: |   |

### 29

This scale is in the public domain

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**Appendix 3**

**PERCEIVED DEFICITS QUESTIONNAIRE - 5-ITEM VERSION (PDQ-5)**

**INSTRUCTIONS**

Everyone at some point experiences problems with memory, attention, or concentration,
but these problems may occur more frequently for individuals with neurologic diseases like MS. The following questions describe several situations in which a person may encounter problems with memory, attention or concentration. If you are marking your own answers, please circle the appropriate response (0, 1, 2,...) based on your cognitive function during the past 4 weeks. If you need help in marking your responses, tell the interviewer the number of the best response. Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

During the past 4 weeks, how often did you....

| Statement                                                                 | Never | Rarely | Sometimes | Often | Almost Always |
|---------------------------------------------------------------------------|-------|--------|-----------|-------|---------------|
| have trouble getting things organized?                                    | 0     | 1      | 2         | 3     | 4             |
| have trouble concentrating on things like watching a television program or reading a book? | 0     | 1      | 2         | 3     | 4             |
| forget the date unless you looked it up?                                 | 0     | 1      | 2         | 3     | 4             |
| forget what you talked about after a telephone conversation?              | 0     | 1      | 2         | 3     | 4             |
| feel like your mind went totally blank?                                  | 0     | 1      | 2         | 3     | 4             |

Appendix 4

Completion of Cognivue® Study Questionnaire

You have completed the research study. Thank you very much for your participation. One of the objectives of this study was to see if this type of testing could be used at each clinic appointment with your neurologist to track your cognitive function over time. Below are questions intended to inform us on how you perceived the Cognivue® testing.

| Never | Rarely | Sometimes | Often | Almost Always |
|-------|--------|-----------|-------|---------------|
| Question                                                                 | 0 | 1 | 2 | 3 | 4 |
|-------------------------------------------------------------------------|---|---|---|---|---|
| Where there any difficulties in using the computer or joystick?        |   |   |   |   |   |
| Would you be willing to perform the computer based testing (Cognivue) at each doctors' appointment? |   |   |   |   |   |

Comments/Suggestions:
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
___________________________________________________________________________________
CONSENT FORM

Evaluation of Cognition in Patients with Multiple Sclerosis Using Cognivue

Principal Investigator: Andrew D Smith III, MD

This consent form describes a research study, what you may expect if you decide to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you agree to participate. You may take this consent form home to think about and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you join this study, you can change your mind and stop at any time.
- If you choose not to take part, your routine medical care will not be changed in any way.
- There are risks from participating and you should understand what these mean to you.

Introduction

You are being asked to take part in this study because you have been diagnosed with Multiple Sclerosis (MS) and are between the ages of 18-50 OR you are a healthy volunteer between the ages of 18-50.
This study is being conducted by Andrew D Smith III, MD of the University of Rochester’s Department of Neurology.

**Purpose of Study**
The purpose of this study is to evaluate a new device, called Cognivue®, a computerized testing system which evaluates cognitive function. We will compare cognitive function in patients with MS to cognitive function in patients without MS.

**Description of Study Procedures**
If you decide to take part in this study, you will be asked to participate in 3 study visits over the next two to 6 months.

At the first visit, we will ask you questions about your medical conditions and treatments; and you will complete a questionnaire called the Hamilton Depression Scale Inventory (HDSI).

If the results of HDSI show that you are eligible for the study, the following procedures will be done:

- You will complete 2 questionnaires.
- You will complete several tests with the Cognivue® system. The Cognivue® testing involves using a joystick to select correct answers on a computer screen. The tests involve letters, words, symbols, direction of movement, and memory. This testing will take about 10 minutes.
- We will also use other tests of cognition including a test where you will add numbers; another where you will decode symbols into digits using a key; and one test where you will place pegs into a pegboard.
- Lastly, we will record a timed 25 foot walk at the first appointment.

Each visit will take approximately 30 minutes.

After the last study visit, we will ask you to complete a short questionnaire about the Cognivue system.

The results of your testing on the Cognivue® system will be stored securely on a USB flash drive. Your name and birthdate will not be included; instead a 4 digit code will be assigned to your test results. These results will then be analyzed on a computer that only study team members will have access to.
**Number of Subjects**
Approximately 60 subjects will take part in this study. Approximately 50% over the subjects will have Multiple Sclerosis and 50% will be healthy volunteers.

**Duration of the Study**
Your participation in the study will last a total of 3-6 months, or when the 3rd testing visit is complete.

**Risks of Participation**
Potential risks of participation include stress related to cognitive testing and possible injury to your dominant arm related to using the cognitive testing system.

Because this study involves collecting personal, identifiable information about you, there is a potential for invasion of privacy or breach in confidentiality. To minimize this risk, we will assign you a study number instead of labeling the information we collect from you with your name [or medical record number]. All of the information we collect will be stored in a secure manner and only study team members will have access to it.

**Benefits of Participation**
You will not benefit from being in this research study.

**New Study Findings**
If we discover anything that might make you change your mind about continuing in the study, we will let you know.

**Sponsor Support**
Cerebral Assessment Systems, Inc – the company that makes the Cognivue system - has donated one *Cognivue* testing system for this study.

**Costs**
There will be no cost to you to participate in this study.
Payments
You will be paid $20 per each study visit that you complete, for a maximum possible total of $60.

You will not receive any money that may result from any commercial tests or products that are developed as a result of this study.

Circumstances for Dismissal
You may be withdrawn from the study if your disease becomes worse or if your doctor feels that staying in the study is harmful to your health.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes
The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will make every attempt to remove personal identifiers as well as store this information in a secure location. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to the study

Who may use and give out information about you?
- The study doctor and the study staff
- URMC and Affiliates
Your information may be given to:
- The Department of Health and Human Services
- The University of Rochester
- Cerebral Assessment Systems Inc, Cognivue Computer
- The U.S. Food and Drug Administration (FDA) may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about you private.

Why will this information be used and/or given to others?
- To do the research
- To study the results
- To see if the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

How long will this permission be valid?
This permission will last indefinitely.

May I cancel my permission to use and disclose information?
Yes. You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
Yes. If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.
Is my health information protected after it has been given to others?
No. There is a risk that your information will be given to others without your permission.

Contact Persons
For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact:
Andrew D. Smith III, MD at 585-275-7854

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420315, Rochester, NY 14642, Telephone (585) 276-0005 or (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached.

Voluntary Participation
Taking part in this study is voluntary. You are free not to take part or to withdraw at any time, for whatever reason. No matter what decision you make, there will be no penalty or loss of benefit to which you are entitled. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

Taking part in this research is not a part of your University duties, and refusing will not affect your job. You will not be offered or receive any special job-related consideration if you take part in this research.

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SIGNATURE/DATES

After reading and discussing the information in this consent form you should understand:
- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to you;
- Other options you may have instead of being in the study;
- How your personal information will be protected;
- What to do if you have problems or questions about this study.

**Subject Consent**

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

__________________________

Subject Name (Printed by Subject)

__________________________  __________

Signature of Subject          Date

**Person Obtaining Consent**

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject’s satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

__________________________

Name and Title (Print)

__________________________  __________

Signature of Person Obtaining Consent          Date
