Title: Impact of Brain Connectome and Personality on Cognitive Rehabilitation in Multiple Sclerosis

Complete Research Protocol (HRP-503)

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Template Instructions

Sections that do not apply:

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.*
    - *For exempt research: Sections 31 and 32 do not apply.*

Studies with multiple participant groups:

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

  Response: N/A

Formatting:

- *Do not remove template instructions or section headings when they do not apply to your study.*

If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.

Amendments:

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

PROTOCOL TITLE:

Include the full protocol title.

Response: Impact of Brain Connectome and Personality on Cognitive Rehabilitation in Multiple Sclerosis

PRINCIPAL INVESTIGATOR:

Name
Department
Telephone Number
Email Address

Response: Ralph H B Benedict PhD

Neurology

859-3484,

benedict@buffalo.edu

VERSION:

Include the version date or number.

Response: Version 1

GRANT APPLICABILITY:

Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.

NOTE: This question does not apply to studies funded by a sponsor contract.

Include a copy of the grant proposal with your submission.

Response: The study is not funded by a grant or award. The funding will be coming from internal funding of Dr. Benedict's lab and BNAC.

RESEARCH REPOSITORY:

Indicate where the research files will be kept, including when the study has been closed. The repository should include, at minimum, copies of IRB correspondence (approval, determination letters) as well as signed consent documents. This documentation should be maintained for 3 years after the study has been closed.

Response: Files are maintained in locked cabinets at the academic offices of Buffalo General Hospital.

Location: Buffalo General Hospital

Address: 100 High Street, Buffalo, NY

Department: Neurology

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research.

Response: The specific aims of this study are:

[1a] Determine whether low Conscientiousness predicts lesser overall cognitive improvement following cognitive rehabilitation in people with MS.

[1b] Determine whether the impact of Conscientiousness on cognitive rehabilitation is moderated by executive function and treatment adherence.

[2] Identify structural and functional brain connectome characteristics which predict successful improvement in sub-domains of cognition following rehabilitation.

This study will also serve to supplement the sample of participants for the current IRB approved study ((IRB: 603069, Title: *A case-control, 5-year follow-up study of cardiovascular, environmental and genetic risk factors for disease progression in patients with multiple sclerosis (CEG-MS study).*

1.2 State the hypotheses to be tested, if applicable.

NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response:

[1a] We expect that individuals with low baseline Conscientiousness will experience a lower magnitude of overall cognitive improvement following rehabilitation

[1b] We expect the impact of Conscientiousness on fidelity of rehabilitation will in part be moderated by individual differences in program adherence and executive function

[2a] We expect that individual differences in structural and functional connectome disturbances will in part explain differences in participant responses to cognitive rehabilitation.

2.0 Scientific Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study.

NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should ***not*** *be a date.*

Response: Our primary end-point are predictive. Our first primary end-point will have been met if baseline measures of personality, as measured by the NEO-Five Factor Inventory (NEOFFI), will predict overall cognitive improvement following rehabilitation. Likewise, our second primary end-point will have been met if baseline measures of brain connectivity predict specific improvements in cognitive sub-domains, following rehabilitation. Cognitive improvement will be measured according to changes from visit 1 to visit 2 for the following neuropsychological tests: Symbol Digit Modalities Test (SDMT), California Verbal Learning Test 2nd Edition (CVLT), Brief Visuospatial Learning Test Revised (BVMT-R), MS Neuropsychological Screening Questionnaire (MSNQ), Delis-Kaplan Executive Function System (DKEFS) Sorting Test, Tower of London (TOL), Elithorn's Perceptual Maze Test (EPMT).

	Day 0 (Visit 1)	Day 90 (Visit 2)
NEO Five Factor Inventory (NEO-FFI)	X	X
Symbol Digit Modalities Test (SDMT)	X	X
California Verbal Learning Test Second Edition (CVLT)	X	X
Brief Visuospatial Memory Test Revised (BVMT)	X	X
MS Neuropsychological Screening Questionnaire (MSNQ)	X	X
Delis Kaplan Executive Function System Tower Test (DKEFS-TT)	X	X
Delis Kaplan Executive Function System Sorting Test (DKEFS-ST)	X	X
Elithorn's Perceptual Maze Test (EPMT)	X	X
Multiple Sclerosis Quality of Life (MSQoL)	X	X
Beck Depression Inventory Fast Screen (BDI-FS)	X	X
Fatigue Severity Scale (FSS)	X	X

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.

Response: The personality trait Conscientiousness is a behavioral phenotype encompassing the proclivity for achievement striving, organization, and deliberation in daily activity. Trait Conscientiousness is operationally measured using the NEO Five Factor inventory (NEOFFI), a model of personality widely studied in MS and other neurological populations.[1] Trait Conscientiousness is normally distributed in humans, shows substantial cross-observer agreement, and has a similar mean and range across different cultures.[2,3]

Decreased Conscientiousness relative to healthy controls (HCs) has been observed in people with multiple sclerosis (pwMS)[4], an autoimmune disease that involves both neuroinflammation and neurodegeneration.[5] It is important to study Conscientiousness decline in pwMS because preliminary findings suggest that **Conscientiousness predicts poor adaptation and unfavorable disease outcomes in neurological disease**. For instance, Conscientiousness predicts CD4 count and viral load over 1-year in HIV disease.[6] Lower Conscientiousness is associated with increased risk of amnestic mild cognitive impairment, and transition to Alzheimer's dementia over 12 years.[7] This trait also correlates negatively with mortality risk among older adults following stroke.[8] Low baseline Conscientiousness is also associated with increased risk of poor disease outcomes in non-neurological diseases. For instance, adults with prediabetes and low Conscientiousness are more likely to later develop type II diabetes, and children with type I diabetes and low Conscientiousness exhibit worse glycemic control.[9,10] Notably, **low Conscientiousness is also associated with reduced success of behavioral interventions on health behaviors and disease outcomes**. For example, low Conscientiousness is prospectively associated with reduced improvement in medication adherence, emotional burden, and physical activity, following a range of behavioral interventions in adults with diabetes.[11]

Lower trait Conscientiousness may also predict less favorable disease course and response to intervention in pwMS. In cross-sectional studies, lower Conscientiousness correlates with impaired processing speed, the hallmark of MS associated cognitive impairment.[12] Low conscientiousness also predicts transition for employment to disability, after controlling for the influence of other factors such as cognitive impairment and depression.[13,14]

The association between low Conscientiousness and poor functional outcomes in pwMS may be due to differences in behavior, such as reduced adherence to disease modifying therapies.[15] Results from a study in people with Alzheimer's disease implicates a role of executive function, moderating the effect of Conscientiousness of disease outcomes.[16] The impact of low Conscientiousness on successful behavioral intervention in pwMS remains unstudied. One investigation of pwMS showed a correlation between reduced success of cognitive training and poor adherence.[17] Thus, we hypothesize that poor adherence and differences in moment-to-moment intention during similar training interventions would be a function of low baseline Conscientiousness. One study validates

this hypothesis, showing that HCs with low Conscientiousness experience reduced near and far transfer effects following a working memory training.[18]

In addition to the application of personality measures, studies have also shown that baseline patterns of brain connectivity can be applied to predict cognitive improvement following training in neurologic disease populations.[19] There is growing interest in the study and application of structural and functional brain network measures in neurologic disease[20] and its relationship with cognitive remediation.[21]

Our goals for this research are two-fold. First, we aim to demonstrate the value of personality assessment as a means of risk-stratification and for directing behavioral interventions in pwMS. In order to address our first goal, we will investigate the value of personality assessment as a means of predicting successful behavioral interventions. In our analysis, we will study whether or not the impact of baseline Conscientiousness on successful cognitive intervention is moderated by other behavioral variables, such as program adherence and executive function, higher order reasoning.

In order to address our second goal, we will use a multi-parametric approach in which we account for cerebral pathology, such as regional gray matter atrophy, microstructural white matter damage, lesion volume and localization, white matter tract integrity and structural connectivity, and resting state functional connectivity. We will apply network-based analysis, where appropriate, in order to account for network-level organization of the brain. These methods of analysis are well-suited for elucidating patterns of insult which lead to changes in complex emergent phenomenon such as higher level cognition.

Our results may provide foundation for better directing rehabilitation and behavioral treatments. For instance, a short questionnaire could be used to identify patients whose personality profile puts them at greater risk for unfavorable disease progression. An understanding of this risk could help direct efforts which mitigate against these unfavorable outcomes. Similarly, baseline patterns of cerebral pathology could also be employed to predict responses the cognitive and other behavioral interventions. There is a burgeoning interest in personality trait adaptation and personalized health plans among health care agencies[22] and we believe our research will contribute meaningfully to this growing field of interest.

3.2 Include complete citations or references.

Response:

1. Costa PT, McCrae RR. Professional manual of the revised NEO personality inventory and NEO five-factor inventory. *Psychol Assess Resour Odessa, FL*. 1992.
2. McCrae RR. Trait psychology and culture: exploring intercultural comparisons. *J Pers*. 2001;69(6):819-846.
3. McCrae RR, Costa PT. Validation of the five-factor model of personality across instruments and observers. *J Pers Soc Psychol*. 1987;52(1):81-90. doi:10.1037/0022-3514.52.1.81.

4. Benedict RHB, Ph D, Priore RL, et al. Personality Disorder in Multiple Sclerosis Correlates with Cognitive Impairment. 2001:70-76.

5. Hauser SL, Oksenberg JR. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. *Neuron*. 2006;52(1):61-76.

6. O'Cleirigh C, Ironson G, Weiss A, Costa Jr. PT. Conscientiousness predicts disease progression (CD4 number and viral load) in people living with HIV. *Heal Psychol*. 2007;26(4):473-480. doi:10.1037/0278-6133.26.4.473.

7. Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. *Arch Gen Psychiatry*. 2007;64(10):1204-1212.

8. Jokela M, Pulkki-Raback L, Elovainio M, Kivimaki M. Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies. *J Behav Med*. 2014;37(5):881-889.

9. Jokela M, Elovainio M, Nyberg ST, et al. Personality and risk of diabetes in adults: Pooled analysis of 5 cohort studies. *Heal Psychol*. 2014;33(12):1618-1621. doi:10.1037/hea0000003.

10. Vollrath ME, Landolt MA, Gnehm HE, Laimbacher J, Sennhauser FH. Child and parental personality are associated with glycaemic control in Type 1 diabetes. *Diabet Med*. 2007;24(9):1028-1033.

11. Fisher L, Hessler D, Masharani U, Strycker L. Research : Educational and Psychological Aspects Impact of baseline patient characteristics on interventions to reduce diabetes distress : the role of personal conscientiousness and diabetes self-efficacy. 2014:739-746. doi:10.1111/dme.12403.

12. Benedict RHB, Schwartz CE, Duberstein P, et al. Influence of personality on the relationship between gray matter volume and neuropsychiatric symptoms in multiple sclerosis. *Psychosom Med*. 2013;75(3):253-261. doi:10.1097/PSY.0b013e31828837cc.

13. Strober LB, Christodoulou C, Benedict RHB, et al. Unemployment in multiple sclerosis : the contribution of personality and disease. 2012. doi:10.1177/1352458511426735.

14. Benedict RHB, Wahlig E, Bakshi R, et al. Predicting quality of life in multiple sclerosis : accounting for physical disability , fatigue , cognition , mood disorder , personality , and behavior change. 2005;231:29-34. doi:10.1016/j.jns.2004.12.009.

15. Bruce JM, Hancock LM, Arnett P, Lynch S. Treatment adherence in multiple sclerosis: Association with emotional status, personality, and cognition. *J Behav Med*. 2010;33(3):219-227. doi:10.1007/s10865-010-9247-y.

16. Roy S, Ph D, Ficarro S, et al. Executive Function and Personality Predict Instrumental Activities of Daily Living in Alzheimer Disease. *Am J Geriatr Psychiatry*. 2017;24(11):1074-1083. doi:10.1016/j.jagp.2016.06.014.

17. Charvet LE, Yang J, Shaw MT, et al. Cognitive function in multiple sclerosis improves with telerehabilitation : Results from a randomized controlled trial.

2017:1-13.

18. Studer-luethi B, Jaeggi SM, Buschkuehl M, Perrig WJ. Influence of neuroticism and conscientiousness on working memory training outcome. *Pers Individ Dif*. 2012;53(1):44-49. doi:10.1016/j.paid.2012.02.012.

19. Arnemann KL, Chen AJ-W, Novakovic-Agopian T, Gratton C, Nomura EM, D'Esposito M. Functional brain network modularity predicts response to cognitive training after brain injury. *Neurology*. 2015;84(15):1568-1574. doi:10.1212/WNL.0000000000001476.

20. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*. 2010;52(3):1059-1069. doi:10.1016/j.neuroimage.2009.10.003.

21. Takeuchi H, Sekiguchi A, Taki Y, et al. Training of Working Memory Impacts Structural Connectivity. 2010;30(9):3297-3303. doi:10.1523/JNEUROSCI.4611-09.2010.

22. Chapman BP, Hampson S, Clarkin J. Personality-Informed Interventions for Healthy Aging: Conclusions From a National Institute on Aging Workgroup Benjamin. 2014;50(5):1426-1441. doi:10.1037/a0034135.Personality-Informed.

4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).

Response: Interventional

5.0 Local Number of Subjects

5.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.

Response: We will recruit 50 subjects with multiple sclerosis who are already enrolled in CEG-MS study.

5.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).

Response:

We expect that potential participants to be enrolled through the CEG-MS study for suitability for the study. Subjects who agree to participate and pass screening requirements will be enrolled in the study.

5.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: This research will be conducted through the Buffalo Neuroimaging Analysis Center (BNAC) group. We expect to recruit subjects from the CEG-MS study database. Based on our targeted population, we believe there is a sufficient number of potential participants to meet participant target of 50 in adherence to the protocol.

6.0 Inclusion and Exclusion Criteria

*6.1 Describe the criteria that define who will be **included** in your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

For all subjects:

- males and females above age 18
- fluent in English
- education >9 years

Additional inclusion criteria for MS patients are as follows:

- Clinically definite MS diagnosis
- Expanded Disability Status Scale (EDSS) ≤ 6.5
- MS patients must be relapse-free and stable from the time of their MRI acquired for the CEG-MS study
- Willing and able to comply with the study procedures for the duration of the trial

*6.2 Describe the criteria that define who will be **excluded** from your final study sample.*

NOTE: This may be done in bullet point fashion.

Response:

- history of serious medical or psychiatric illness (other than MS in the patient group) that may affect cognitive functioning
- color-blindness

- history of developmental disability
- past or current alcohol or substance dependence
- History of major depressive disorder, bipolar disorder, or psychotic disorder predating the onset of MS
- History of traumatic brain injury as defined by trauma causing loss of consciousness or transient post-traumatic or retrograde amnesia exceeding 5 min
- Other pathology related to MRI abnormalities

6.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.

NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.

Response:

☒ Adults unable to consent

☒ Individuals who are not yet adults (infants, children, teenagers)

☒ Pregnant women

☒ Prisoners

6.4 Indicate whether you will include non-English speaking individuals in your study. ***Provide justification if you will exclude non-English speaking individuals.***

In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may ***not*** *be routinely excluded from research as a matter of convenience.*

In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.

Response: Non-English speaking individuals will not be able to have a neuropsychological assessment battery administered as measures are developed in English and no translations are available. Thus non-English speaking individuals will not be involved in the research.

7.0 Vulnerable Populations

If the research involves special populations that are considered vulnerable, ***describe the safeguards included to protect their rights and welfare.***

NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.

7.1 For research that involves ***pregnant women,*** *safeguards include:*
NOTE CHECKLIST: Pregnant Women (HRP-412)

Response:

☒ **N/A**: This research does not involve pregnant women.

7.2 For research that involves ***neonates of uncertain viability or non-viable neonates,*** *safeguards include:*
NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves ***prisoners****, safeguards include:*
NOTE CHECKLIST: Prisoners (HRP-415)

Response:

☒ **N/A:** This research does not involve prisoners.

7.4 For research that involves ***persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")****, safeguards include:*
NOTE CHECKLIST: Children (HRP-416)

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

7.5 For research that involves ***cognitively impaired adults****, safeguards include:*
NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)

Response:

☒ **N/A:** This research does not involve cognitively impaired adults.

7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. ***Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response: N/A

8.0 Eligibility Screening

8.1 Describe ***screening procedures*** *for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).

Response:

All subjects will be recruited from the CEG-MS study. Subjects will undergo eligibility screening conducted by trained members of the research team using the attached phone and in-person script, and screening form to determine whether or not they are interested and meet all of the eligibility criteria outlined above.

Please see attached.

9.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

9.1 Describe when, where, and how potential subjects will be recruited.

NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).

Response:

Potential participants will be identified from the pre-existing list of study participants of the CEG-MS study database. Recruitment will be directed towards subjects who completed MRI evaluation for the CEG-MS study. These individuals will then be further screened based on the inclusion and exclusion criteria and contacted in person and via phone. If they are interested, the remaining screening questions will be asked. If the individual agrees to participate in the study, their appointment for testing will be scheduled based on their availability and convenience.

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.

NOTE: Privacy refers to an individual's right to control access to him or herself.

Response:

Contact information from CEG-MS study databases is retained on a secure network in Buffalo Neuroimaging Analysis Centre (BNAC). The network is password protected and can only be accessed by PI and trained study members. Information is de-identified within the contact information file and only those with access to both that file and a separate de-identifying key file called 'CEG Codes' will be able to link the potential participant's name to his/her contact information. Once a participant has been recruited, his/her information will be removed from the recruitment contact information file.

9.3 Identify any materials that will be used to recruit subjects.

NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.

For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.

Response:

Please see attached phone and in-person script.

10.0 Procedures Involved

*10.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.

Response:

The participant will be asked to make a total of two (2) visits, approximately 90 days apart. Each visit will involve: neuro-performance testing, and self-report questionnaires. Each study visit is expected to take approximately 1-2 hours. Between the two visits, the participant will be asked to complete a 12 week, computer-based cognitive training program. This includes 1 hour of training each day for 5 days each week.

On Visit 1, the participants will undergo a full battery of neuro-performance tasks including tests and questionnaires that measure your memory, thinking speed, fatigue, and personality. This visit is expected to take approximately 1-2 hours. The participants will be also asked to have a close friend or family member to complete similar surveys. A self-addressed envelope containing these questionnaires will be provided to take home with them. The participant will need to pass it onto a close friend or family member to be completed and mailed back.

In addition, the participant will be asked to take part in the 12 week computerized cognitive training program. This can be done at home, or anywhere the participant has access to a computer and internet. This cognitive training has been shown to improve cognitive performance in people with multiple sclerosis. The training involves a variety of interactive exercises which adapt to your abilities. The participants will need complete 1 hour of training each day, for 5 days each week.

At 90 days, the participant will return for the 1-2 hours' follow-up visit where they will complete the same cognitive testing and questionnaires which they had completed during visit 1.

All study visits will take place at Buffalo General Hospital. All of the procedures described above will be performed by a trained member of the research team as part of the research study.

If an individual is ineligible for participation, their screening information will be discarded (i.e., shredded). If participants are deemed eligible (either in person or over the phone), they will be scheduled to come in to the hospital for neuropsychological testing. Written consent will be obtained prior to administration of tests. As part of the consent process, participants will be asked for permission to use any data collected as part of the screening process as well.

10.2 Describe what data will be collected.

NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

Response: Demographic/social history, health history (as provided by participants during screening, review of medical records, etc.), and cognitive test data.

10.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).

Include copies of these documents with your submission.

Response: Below is a list of neuropsychological tests that will be included. Symbol Digit Modalities Test (SDMT), California Verbal Learning Test 2nd Edition (CVLT), Brief Visuospatial Learning Test Revised (BVMT-R), Delis-Kaplan Executive Function System [DKEFS] Sorting Test, Delis-Kaplan

Executive Function System [DKEFS] Tower Test. Self-report/informant-report surveys have been uploaded. Self-report measures include the Beck Depression Inventory-Fast Screen (BDI-FS), Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), Fatigue Severity Scale (FSS), NEO-FFI personality inventory, Multiple Sclerosis Quality of Life (MSQoL) and Elithorn's Perceptual Maze Test (EPMT). Informant-report measures include the NEO-FFI.

10.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).

Response: We will be collecting MRI and EDSS information for subjects from the database of IRB no. 603069 of CEG- MS study.

*10.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: In case of any incidental findings, the details will be shared with subject's primary care physician by adhering to the procedures and reporting policies as outlined by the UBIRB. Results will not be shared with participants or anyone else. Any incidental findings for the patients will be relayed to the primary neurologist who can make the determination regarding whether to share this information with the participant's primary care physician.

*10.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: Study results will not be shared with subjects.

11.0 Study Timelines

11.1 Describe the anticipated duration needed to enroll all study subjects.

Response: It is anticipated that enrollment of all study subjects will be completed in one to one-and-a-half years.

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response:

Patients will complete two visits (Day 1 and Day 90). Neuropsychological testing will take approximately 1-2 hours during a single visit.

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response:

Completion of this study, including primary analyses is expected to be in one to two years.

12.0 Setting

12.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."

Response: Screening and neuropsychological procedures will be conducted in a private testing room in the Buffalo Neuroimaging Analysis Center (BNAC) at the Buffalo General Hospital. Database entry and data analysis will also occur at the academic offices of Buffalo Neuroimaging Analysis Center (BNAC).

12.2 For research conducted outside of UB and its affiliates, describe:

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.

Response:

☒ **N/A:** This study is not conducted outside of UB or its affiliates.

13.0 Community-Based Participatory Research

13.1 Describe involvement of the community in the design and conduct of the research.

NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a

research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

Response:

☒ **N/A:** This study does not utilize CBPR.

13.2 Describe the composition and involvement of a community advisory board.

Response:

☒ **N/A:** This study does not have a community advisory board.

14.0 Resources and Qualifications

*14.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.

Response: Ralph Benedict is a board-certified neuropsychologist. All members of the research team will receive extensive training to administer study procedures in this research. They will also undergo required CITI and UBIRB GCP training. They will also be closely supervised by Ralph Benedict.

Describe other resources available to conduct the research.

14.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.

NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.

Response: The PI will be adequately accessible to oversee this project. In addition, members of the research team will be dedicated to conducting the project.

14.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.

NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.

Response: While there are no anticipated consequences, the PI will be adequately accessible to address any needs. Any unanticipated medical emergencies or incidental findings will be brought to the attention of a neurologist responsible for the care of the patient.

14.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response:

As described above, all research staff will undergo extensive training in administration of neuropsychological tests and they will be closely supervised by neuropsychologist, Dr. Ralph Benedict. They will also be required to undergo all necessary research training protocols before engaging in research activities with participants.

15.0 Other Approvals

15.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).

Response:

☒ **N/A:** This study does not require any other approvals.

16.0 Provisions to Protect the Privacy Interests of Subjects

16.1 Describe how you will protect subjects' privacy interests during the course of this research.

NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.

Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response:

Study procedures are performed in private, noise- and temperature-controlled rooms and will be conducted in the presence of only one designated, trained member of the research team. Study documents are maintained in a locked staff office that is only accessed by designated personnel. Participants are reminded that they are free to refuse to answer any questions at any time. When they contact the research team via telephone they are able to determine the privacy of the settings in which they participate.

16.2 Indicate how the research team is permitted to access any sources of information about the subjects.

NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question ***does apply*** *to records reviews.*

Response:

After the consent process, the participant controls the research team's access to such information because it was directly provided by the participant through an interview/survey procedure.

17.0 Data Management and Analysis

17.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response:

Statistical analyses will be performed using SPSS 22.0 (IBM Inc., Armonk, NY, USA) and R 3.4.1 (The R Foundation).

[1a] Determine whether low Conscientiousness predicts lesser overall cognitive improvement following cognitive rehabilitation in people with MS. The question of whether Conscientiousness predicts successful intervention will be addressed using baseline measures of trait Conscientiousness and cognitive performance before and after rehabilitation. We will assess linear relationships between baseline trait Conscientiousness and overall magnitude of cognitive improvement using linear regression models. Cognitive improvement will be measured according to differences in cognitive scores between baseline assessment during visit 1 and post-rehabilitation assessment at visit 2. In order to summarize results across all cognitive measures, test scores will be converted to normalized z-scores and averaged together.

1b] Determine whether the impact of Conscientiousness on cognitive rehabilitation is moderated by executive function and treatment adherence. In order to address the question of whether or not adherence and executive function moderate the impact of Conscientiousness on intervention success, we intend to add interaction parameters to the linear regression analysis described for aim 1a.

For instance, we will calculate the interaction variable between Conscientiousness and DKEFS-ST (executive function) and include it in our regression models.

[2] Identify structural and functional brain connectome characteristics which predict successful improvement in sub-domains of cognition following rehabilitation. In order to identify brain connectome characteristics which, predict specific responses to sub-domains of cognition following rehabilitation, we intend to employ linear machine/statistical learning techniques, such as partial least squares regression. The correct statistical learning models will be identified at the time of analysis in order to produce the most appropriate predictions. Models will be selected according to the distribution and dimensionality of our connectome variables. Following training of the predictive models, fit of the models will be assessed using k-fold cross validation.

17.2 If applicable, provide a power analysis.

NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: Given a 0.38 effect size observed in a previous study of HCs which indicated a relationship between Conscientiousness and successful cognitive training[20], power analysis indicated 41 participants would be sufficient for an 80% chance of avoiding type II error.

17.3 Describe any procedures that will be used for quality control of collected data.

Response:

All MRI data has already been reviewed for quality by expert investigators responsible for the CEG-MS study.

Scoring and data entry will be completed and checked by trained staff members under the supervision of the PI.

18.0 Confidentiality

A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

18.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls,

authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) ***and*** *electronic files.*

Response: Neuropsychological testing data and clinical outcome measures will be maintained in de-identified participant charts. These charts will be stored in a locked cabinet and entered into a password-protected database. Appropriate legal guidelines regarding retention of records will be followed. Identifiable data will be destroyed at the earliest possible point. The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential. Stored data will be accessed only by the PI and/or designated research staff. The use of stored, de-identified data is undetermined at this time.

18.2 A. How long will the data be stored?

Response: Data will be stored for the duration of the study and according to federal regulations.

18.3 A. Who will have access to the data?

Response: The principal investigator and delegated research staff.

18.4 A. Who is responsible for receipt or transmission of the data?

Response: The principal investigator and delegated research staff.

18.5 A. How will the data be transported?

Response: Data will not be transported locally.

B. Confidentiality of Study Specimens

Describe the local procedures for maintenance of confidentiality of ***study specimens****.*

☒ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 19.0)*

18.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response:

18.7 B. How long will the specimens be stored?

Response:

18.8 B. Who will have access to the specimens?

Response:

18.9 B. Who is responsible for receipt or transmission of the specimens?

Response:

18.10 B. How will the specimens be transported?

Response:

19.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.

19.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: Data will be reviewed periodically to confirm the safety of all subjects.

19.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: All data will be reviewed.

19.3 Describe any safety endpoints.

Response: There are no safety endpoints in this study. There is no active medical intervention and the assessments pose no known risk to the subjects.

19.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: N/A

19.5 Describe the frequency of safety data collection.

Response: N/A

19.6 Describe who will review the safety data.

Response: N/A

19.7 Describe the frequency or periodicity of review of cumulative safety data.

Response: N/A

19.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: N/A

19.9 Describe any conditions that trigger an immediate suspension of the research.

Response: N/A

20.0 Withdrawal of Subjects

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*20.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: Participation in this study is voluntary. Patients are explicitly informed that that they may withdraw from the study at any time and for any reason. Additionally, if, in the opinion of the site PI that a subject is no longer able to provide informed consent, or if a subject is non-compliant with study visits he/she may be withdrawn from the study. For example, if more than three attempts to contact the patient to schedule any study-related procedure are unsuccessful, the patient may be withdrawn

20.2 Describe any procedures for orderly termination.

NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: In the event of early termination/withdrawal from the study, an exit interview will be conducted by the PI, treating clinician or trained members of the research team.

20.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: Participation in this study is voluntary. Referred patients may refuse to participate without penalty and such refusal will not prejudice future treatment or benefits at the Jacobs Neurological Institute (JNI) or Buffalo Neuroimaging Analysis Center (BNAC). Patients will be free to discontinue participation in the study at any time without fear of penalty or loss of medical care or loss of any benefits to which you may otherwise be entitled. If a subject chooses to withdraw from the study, the data collected up to the time of withdrawal will continue to be used, but the subject will no longer be contacted and no further data will be collected.

21.0 Risks to Subjects

21.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.

NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response: The only foreseeable risk is breach of confidentiality, although this is unlikely to occur. Since subjects are being asked to perform cognitive and manual tasks as part of this study, however, they may experience some stress or anxiety or fatigue associated with mental and physical exertion. There are no social, legal, or economic risks.

21.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: N/A

*21.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response: Subjects are being asked to perform cognitive and manual tasks and some may experience psychological stress/pressure/anxiety or mental fatigue with such exertion.

21.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: N/A

21.5 If applicable, describe risks to others who are not subjects.

Response: There are no anticipated risks to others who are not subjects.

22.0 Potential Benefits to Subjects

22.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.

*NOTE: Compensation **cannot** be stated as a benefit.*

Response: Participants who successfully adhere to the study protocols are expected to experience improved cognitive performance and perceived cognition.

23.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*23.1 **If the research procedures carry a risk of research related injury,** describe the available compensation to subjects in the event that such injury should occur.*

Response: The University at Buffalo has no program to pay for medical care for research-related injury. No injuries are expected.

23.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.

*NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: N/A

24.0 Economic Burden to Subjects

24.1 Describe any costs that subjects may be responsible for because of participation in the research.

NOTE: Some examples include transportation or parking.

Response:

The subject is not responsible for any costs of the procedures involved in the study.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

25.0 Compensation for Participation

25.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.

Response: Subjects will receive $50 compensation for completion of each study visit. Checks will be mailed to subjects.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

26.0 Consent Process

26.1 Indicate whether you will be obtaining consent.

NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*
☐ ***No*** *(If no, Skip to Section 27.0)*

26.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.

Response: The consent process will take place in a private, temperature and noise controlled testing room in BNAC, Department of Neurology, Buffalo General Hospital.

26.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.

NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.

Response: Consent will be provided in-person prior to neuropsychological assessment at a point where the PI or his representative is available to answer any questions about the study.

26.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: Prior to all study-related procedures participants will reminded that participation is voluntary.

26.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:

- *The role of the individuals listed in the application who are involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

Non-English Speaking Subjects

☒ **N/A:** This study will not enroll Non-English speaking subjects. *(Skip to Section 26.8)*

26.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.

Response: N/A

26.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."

Response: N/A

Cognitively Impaired Adults

☒ **N/A**: This study will not enroll cognitively impaired adults.
(Skip to Section 26.9)

26.8 Describe the process to determine whether an individual is capable of consent.

Response: Individuals are deemed capable when they express an understanding of the study objectives, procedures, etc. Understanding of the study procedures, objectives, etc will be determined if the subject is able to coherently relay relevant information when asked by the research staff.

Adults Unable to Consent

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10) ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

26.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.

NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

26.10 ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response: N/A

26.11 Describe the process for ***assent of the adults****:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.*

Response:

- *If assent will not be obtained from some or all subjects, provide an explanation of why not.*

Response:

26.12 Describe whether ***assent of the adult*** *subjects will be documented and the process to document assent.*

NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.

Response:

Subjects who are not yet Adults (Infants, Children, and Teenagers)

☒ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

26.13 Describe the criteria that will be used to determine ***whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research*** *under the applicable law of the jurisdiction in which the research will be conducted* ***(e.g., individuals under the age of 18 years)****. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.

Response:

26.14 ***For research conducted outside of New York State****, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

26.15 Describe whether parental permission will be obtained from:

Response:

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."

26.16 Describe whether permission will be obtained from individuals ***other than parents****, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response:

26.17 Indicate whether assent will be obtained from all, some, or none of the ***children****. If assent will be obtained from some children, indicate which children will be required to assent.*

Response:

26.18 When assent of children is obtained, describe how it will be documented.

Response:

27.0 Waiver or Alteration of Consent Process

Consent will not be obtained, required information will not be disclosed, or the research involves deception.

☒ **N/A:** A waiver or alteration of consent is not being requested.

27.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.

NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.

Response:

27.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

28.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
(Skip to Section 29.0)

28.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.

If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).

Response: Consent form is included in the application packet

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

29.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*29.1 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as:*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

29.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

Response:

29.3 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.

Response:

29.4 If this is a multicenter study for which UB will serve as the IRB of record, and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods.

Response:

30.0 Banking Data or Specimens for Future Use

☐ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*30.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).

Response: The data will be maintained indefinitely.

30.2 List the data to be stored or associated with each specimen.

Response: Data collected from the research-related procedures described above will be stored.

30.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: Data will not be released to those outside the clinical treatment or research team.

31.0 Drugs or Devices

☒ **N/A:** This study does not involve drugs or devices. This section does not apply.

31.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response:

31.2 Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response:

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

31.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response:

31.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response:

32.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

32.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

32.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: