A. SPECIFIC AIMS

**AIM 1.** To conduct a comprehensive longitudinal evaluation of neurocognitive function in HIV-positive women. (Led by J. Manly and E. Martin)

**Aim 1.1.** To determine if HIV-positive women experience more rapid age-related decline in a range of cognitive abilities as compared to risk-control-matched, HIV-negative women.

- **Hypothesis 1.1.1.** HIV-positive women will experience a more rapid age-related decline in speed, executive function, and memory.

**Aim 1.2.** To determine how the rate of cognitive change is influenced by the unique and synergistic effects of sociodemographics, substance misuse, laboratory indices of HIV disease severity, additional medical and psychiatric co-morbidities, and to determine whether these associations differ from those seen among HIV-positive women.

- **Hypothesis 1.2.1.** Fewer years of education; poorer quality of education, as estimated by reading achievement; lower estimated IQ; minority race/ethnicity; and increased age will predict faster rates of decline in working memory and verbal learning and memory over time.

- **Hypothesis 1.2.2.** Depressive symptoms, substance abuse, immunologic function, health, and exposure to antiretroviral therapy, analyzed as time-dependent covariates, will be independently associated with more rapid decline in executive function, learning efficiency, and delayed memory.

**Aim 1.3.** To investigate the normal range of scores on neuropsychological tests representing various cognitive domains among HIV-uninfected women and to determine: (1) cutoffs that define neuropsychological dysfunction after adjusting for the role of age and educational experience on test performance, and (2) definitions of asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).

**AIM 2.** To characterize the impact of negative life events and self-reported post-traumatic stress disorder (PTSD) symptoms on increased vulnerability for neuropsychological dysfunction in HIV-infected and at-risk HIV-uninfected women. (Led by C. Smith, K. Weber and P. Maki)

**Aim 2.1.** To characterize the relationship between PTSD symptoms and neuropsychological test performance in HIV-positive and at-risk seronegative women.

- **Hypothesis 2.1.1.** The presence of clinically significant symptoms of PTSD will predict worse episodic memory, and the magnitude of this effect will be greater for HIV-infected versus HIV-uninfected women.

- **Hypothesis 2.1.2.** A history of negative life events, which includes childhood and/or sexual, physical, and emotional abuse, will predict worse episodic memory, and the magnitude of this effect will be greater for HIV-infected versus HIV-uninfected women.
Hypothesis 2.1.3. Having experienced a greater number of negative life events will predict poor performance on measures of executive functioning, and the magnitude of this effect will be greater for HIV-positive versus HIV-negative women.

Aim 2.2. To examine the contribution of childhood trauma on the development and persistence of clinically significant symptoms of PTSD and depression in HIV-infected and HIV-uninfected women.

Hypothesis 2.2.1. HIV-infected women with a history of childhood trauma are at increased risk for clinically significant symptoms of depression and PTSD.

AIM 3. To better understand the impact of menopausal stage, menopausal symptoms, and ovarian steroids on psychological health, cognition, and functional status in HIV-infected and HIV-uninfected women. (Led by P. Maki)

Aim 3.1. To examine the frequency and severity of menopausal symptoms in HIV-infected and HIV-uninfected women as a function of menopausal stage.

Hypothesis 3.1.1. Vasomotor symptoms, psychological symptoms, insomnia, and genitourinary symptoms will be more common among midlife HIV-positive women compared with midlife HIV-negative women, particularly as women transition from the premenopausal stage to the perimenopausal stage.

Aim 3.2. To determine the extent to which the rate of decline in verbal memory and executive function is influenced by menopausal stage and menopausal symptoms.

Hypothesis 3.2.1. Verbal memory and verbal fluency will worsen as women transition from the pre- to perimenopausal stage, even after controlling for age, disease progression, and other confounding factors.

Aim 3.3. To examine depressive symptoms in HIV-infected and HIV-uninfected women in relation to menopausal stage, and to relate this change in mood to change in cognition.

Hypothesis 3.3.1. Both groups will show a significant increase in depressive symptoms as they transition from pre- to perimenopause.

Hypothesis 3.3.2. The worsening of depressive symptoms during perimenopause will be related to a decrease in verbal memory and increase in executive dysfunction.

Hypothesis 3.3.3. Severe perimenopausal depressive symptoms will relate to harmful behaviors (e.g., substance use and worse self-reported parenting skills).

Aim 4. To characterize sociodemographic, behavioral, and cognitive predictors of functional outcomes that are particularly relevant for HIV-infected women. (Led by K. Weber and R. Schwartz)

Hypothesis 4.1. Overall and domain specific neurocognitive impairment and rate of cognitive decline will predict onset and severity of gender- and HIV-related functional disabilities, and this relationship will be moderated by household structure or functional and community factors.
**Hypothesis 4.2.** Lower socioeconomic status, substance use, criminal involvement, symptoms of PTSD and depression, higher household burden, and cognitive impairment will predict lower self-ratings of parenting/grandparenting self efficacy and formal loss of child custody in HIV-infected and HIV-uninfected women.

**Hypothesis 4.3.** Higher cognitive performance will predict return to work and maintenance of employment among HIV-uninfected women; however, HIV-infected women will report disincentives for employment including retention of disability income and childcare arrangements that would be barriers to employment even with good cognitive function.

**Hypothesis 4.4.** After controlling for age and substance misuse, compared with HIV-negative women, HIV-positive women will score higher in Quality of Life (QOL) domains for social and role function, have less difficulty performing Instrumental Activities of Daily Living (IADL), report less criminal involvement, report fewer depressive and PTSD symptoms, and report higher self ratings of parenting skills and better maintain child custody; these differences will relate to greater health care utilization and access to support services among HIV-infected women.

**Hypothesis 4.5.** Onset of functional disabilities will predict a more rapid subsequent trajectory of cognitive decline and will relate to decreased time spent outside the home, physical inactivity, and lower IADL scores; this relationship will be moderated by the presence or absence of supportive care provided by household members.

**AIM 5.** To integrate neurocognition and neuropathy data with data from other WIHS working groups to understand the etiology of cognitive decline and neuropathy in HIV-infected women. *(Including past and future contributions from H. Crystal, R. Greenblatt, M. Young, V. Valcour, C. Smith, and other WIHS investigators)*

**Aim 5.1.** To understand the etiology of cognitive decline in WIHS women.

**Aim 5.2.** To understand the prevalence and etiology of neuropathy. *(Led by H. Crystal)*

**Aim 5.2.1.** To understand the prevalence and incidence of neuropathy in WIHS women based on formal objective assessments.

- **Hypothesis 5.2.1.1.** The prevalence and incidence of neuropathy will be increased in relation to HIV and HCV infection status, and age.

**Aim 5.2.2.** To understand the influence of menopausal stage, inflammation, and cardiovascular disease on the prevalence and incidence of HIV-related distal sensory polyneuropathy (DSPN).

- **Hypothesis 5.2.2.1.** Because estrogen reduces neuroinflammation, DSPN will be less frequent (after adjusting for co-morbidities and age) in premenopausal women compared with postmenopausal women.

- **Hypothesis 5.2.2.2.** Although cardiovascular risk factors and inflammation have been associated with cognitive impairment, mechanisms explaining these associations are not fully understood. We hypothesize that risk factors for dysfunction in the central nervous system may also affect the peripheral nervous system and manifest as DSPN.
Aim 5.2.3. To examine the relationship between cognition and DSPN.

- Hypothesis 5.2.3.1. If common mechanisms lead to dysfunction in the central and peripheral nervous systems, then there should be a significant relationship between DSPN and cognition.

B. BACKGROUND AND SIGNIFICANCE

1. **AIM 1.** To conduct a comprehensive, longitudinal evaluation of neurocognitive function in HIV-positive women.

One of the major challenges in prior studies of the neurocognitive effects of HIV infection has been that, cross-sectionally, it is difficult to segregate the impact of HIV on cognitive test scores from the impact of baseline ability and other concomitant conditions or cognitive risk factors. This is especially problematic in cohorts like the WIHS, which includes women who are extraordinarily diverse with respect to educational and cultural background, and where concomitant conditions such as substance use, diabetes, head injury, HCV infection and other risk factors for cognitive decline may also affect test scores. Because participants serve as their own controls in longitudinal studies, these cohort effects can be distinguished from the effects of HIV infection, antiretroviral treatment, and characteristics of immunologic response. Furthermore, for this same reason, longitudinal design is critical to address aims regarding the interaction between HIV infection and age on cognitive function. WIHS is well-poised to conduct a longitudinal study of cognitive function due to a number of reasons: (1) the age distribution of the cohort, (2) the comprehensive information available about predictors and covariates that may relate to cognitive change, (3) the large number of HIV-infected and HIV-uninfected participants, and (4) an infrastructure that can accommodate the addition of neurocognitive assessments into the existing plan for follow-up visits.

The WIHS-IV Neurocognitive Study proposes administration of a reliable, valid battery of cognitive tests to all participants at 24-month intervals. The battery will consist of tests of attention, visuomotor speed, psychomotor speed, reaction time, fine motor speed/coordination, executive function, language, working memory, and learning and recall of novel verbal material. Using the proposed neuropsychological test battery in its entirety, the WIHS is well positioned to incorporate 2007 state-of-the-science nosology for HIV-associated neurocognitive disorders that have been developed by an expert panel of neuroAIDS researchers in order to develop definitions for phenotypes of cognitive impairment. The report of the expert panel emphasizes the critical role of comprehensive neurocognitive data in accurate diagnoses of HIV-associated neurocognitive syndromes. The 2007 neuroAIDS Working Group defined comprehensive assessment batteries to include, at minimum, assessment of the following domains: attention-information processing, language, abstraction-executive function, complex perceptual motor skills, memory (including learning and recall), and simple motor skills or sensory perceptual abilities. Using baseline test performance data from HIV-uninfected women, and after applying these normative standards to the follow-up data, we will define ranges of normal and impaired performance on each cognitive domain. This approach will enable us to determine the best independent and interactive predictors of progression for categories of neurobehavioral function based on level of cognitive impairment. Assessment of cognition across broad domains of function will be emphasized by the Working Group because of the large body of literature demonstrating the clinical significance of a comprehensive battery to predict employment and other critical life tasks. Neurocognitive performance is an independent predictor of survival time and correlates with regional neuropathology post-mortem.

In the primary analyses of predictors of cognitive change, we will examine select WIHS core variables collected at or closest in time to the baseline and follow-up neurocognitive assessments. Available core WIHS predictors, including time-varying covariates and constructed summary variables when appropriate, include: sociodemographics (e.g., age, education, estimated IQ,
race/ethnicity), family characteristics (e.g., marital/partner status, housing stability, household composition), substance misuse, functional status, indices of health related quality of life, laboratory indices of HIV disease severity, and additional medical and psychiatric co-morbidities (e.g., HCV, diabetes, hypertension, cardiovascular events, severe depression, bipolar disorder, antiretroviral use by type and central nervous system (CNS) penetrance, and additional medications used). Analyses will focus on the unique and/or synergistic effects of these predictors, and we will examine both continuous outcomes and categorical clinical outcomes.

2. **AIM 2. To characterize the impact of negative life events and self-reported post-traumatic stress disorder (PTSD) symptoms to increased vulnerability for neuropsychological dysfunction in HIV-infected and at-risk HIV-uninfected women.**

One of the new areas of focus proposed for WIHS-IV is a study of how childhood trauma and clinically significant symptoms of post-traumatic stress disorder (PTSD) and depression influence cognitive performance. A growing body of research demonstrates that earlier age of trauma, chronic repeated stress exposures, and intensity of acute stressors can lead to profound physiological and psychological consequences. Notably, a history of childhood sexual or physical trauma, intense acute stress, or PTSD is associated with an increased risk of HIV-related morbidity and mortality. PTSD is also a strong predictor of injection drug use, and risky sexual behavior particularly in women. WIHS investigations have demonstrated that early childhood abuse leads to later domestic violence, which may increase the risk of behaviors leading to HIV infection, and that childhood abuse is associated with lack of adherence to HAART.

The Neurocognitive Working Group (NCWG) proposes to extend this area of investigation to the study of the impact of stressful life events and symptoms of PTSD on rate of cognitive change. An increasing number of studies identify stress-related structural and functional alterations within the central nervous system (CNS), particularly within the corpus callosum, caudate, anterior cingulate, medial prefrontal cortex, and hippocampus. Clinical correlates, including decreased verbal and visual learning and memory and impaired executive functions, are also reported. As decreased memory and executive functioning are also associated with HIV infection, women living with HIV who also have a history of childhood trauma and/or PTSD as an adult may be especially susceptible to cognitive and psychological dysfunction due to the additive or synergistic effects of HIV and acute/chronic stress. In men, acute stressful life events are known to contribute to poor executive function, attention, and processing speed, yet the additive or synergistic relationship between HIV and stress on cognition has yet to be systematically examined in women.

In order to evaluate the impact of current and cumulative stress on cognitive function in women living with HIV, and to address stress-related aims relevant to the other WIHS cores and projects, we propose administration of a brief self-report PTSD checklist – Civilian Version (PCL-C). While there are many measures of PTSD available for consideration, we have selected this measure specifically due to demonstrated validity, short administration time, and our initial pilot studies in Chicago. In the total WIHS cohort, we will examine the relationships between the severity of clinically significant PTSD symptoms, mood, and cognitive test performance (i.e., especially episodic memory and executive function). WIHS investigators across other projects and cores will concurrently describe prevalence and predictors of stress disorders among WIHS women and effects on HIV-specific and health outcomes and behaviors, service utilization, smoking and substance abuse, gynecologic conditions, and cardiovascular/metabolic disease risk factors.
3. **AIM 3. To better understand the impact of menopausal stage, menopausal symptoms, and ovarian steroids on psychological health, cognition, and functional status in HIV-infected and HIV-uninfected women.**

In healthy women, ovarian steroid hormones influence important aspects of psychological health, including depression and cognitive function. Hormonal fluctuations across the menstrual cycle are associated with changes in cognitive function, particularly on tests that show average sex differences. The immediate cognitive effects of menopausal declines in ovarian hormones are modest; the transition from premenopausal to perimenopausal stage is associated with slight decreases in verbal fluency, but not in working memory or perceptual speed. There is little evidence for an effect of reproductive stage, per se, on cognition; however, menopausal symptoms — particularly mood changes, sleep deprivation, and hot flashes — can negatively impact cognition. In our studies in healthy midlife women, vasomotor symptoms (measured objectively with ambulatory monitors) and sleep deprivation independently predict lower memory performance. Furthermore, the long-term cognitive consequences of ovarian hormone declines at menopause may be significant, as indicated by increased risk of dementia associated with early surgical menopause and evidence that use of hormone therapy early in menopause (though not later) may protect against cognitive decline. The cognitive changes associated with the menopausal transition and onset of menopausal symptoms may be most evident in women with compromised cognitive performance, including HIV-positive women. Despite the wealth of literature on normative changes in women’s health across the menopausal transition, very little is known about the natural history of menopause in HIV-positive women, particularly with regard to psychological and cognitive changes. Cross-sectional studies indicate that, compared to HIV-negative women, HIV-positive women report more menopausal symptoms and may have an earlier age at menopause. There are no longitudinal studies tracking symptoms in HIV-positive women as they transition through the menopause. A Chicago pilot study indicated that ratings of bothersome hot flashes were negatively associated with visual memory and executive function, and these effects remained significant after controlling for age, education, CD4 nadir, and depressive symptoms scores. No significant relationships were found between hormone levels and cognition. These findings provide initial insights into the types of cognitive disturbances associated with menopausal symptoms in HIV-positive women and suggest that interventions that lower vasomotor symptoms may confer cognitive benefit.

The opportunity to longitudinally investigate menopause and menopausal symptoms in WIHS is significant, but identifying menopausal stage and symptoms in this population is challenging. First, the standard criteria for identifying menopausal stage in healthy women rely on patterns of amenorrhea. Data from WIHS, however, demonstrate that HIV-positive women experience long periods of amenorrhea in the absence of ovarian failure. Thus, for healthy women, the absence of menses may be a reliable indicator of reproductive stage, but for HIV-positive women, the absence of menses does not necessarily indicate a transition to a later reproductive stage. Staging of reproductive phase in HIV is further challenged by factors that are associated with early age at menopause, such as smoking, lower socioeconomic status, and drug use. To address this challenge, the NCWG will work with WIHS investigators who are spearheading attempts to use novel biomarkers, such as Anti-Müllerian Hormone (AMH), to identify reproductive stage in HIV-positive and -negative women.

The second challenge is to correctly identify menopausal symptoms in HIV-positive women; this is complicated by the fact that many symptoms associated with the menopausal transition overlap with symptoms of HIV and its treatment, including changes in mood and memory, hot flashes, and sleep disturbance. The NCWG will examine menopausal symptoms as a function of menopausal stage in order to identify symptoms that increase as women transition from premenopausal to perimenopausal stages. We will continue to collect self-reported symptoms of...
menopause at every six-month visit, in order to test hypotheses that do not pertain directly to cognitive aims, using a questionnaire comprised of selected questions from: (1) revised criteria obtained via personal correspondence with the primary author of the Staging of Reproductive Aging Workshop (STRAW), a workshop aimed at developing a staging system for female reproductive aging; (2) the Study of Women’s Health Across the Nation (SWAN), a National Institutes of Health funded, multisite, longitudinal study of the natural history of midlife women, including the menopausal transition; and (3) The Baltimore Longitudinal Study on Aging (BLSA), which set out to measure physiological and psychological functions in healthy community-living volunteers over long periods of time.

4. **AIM 4. To characterize sociodemographic, behavioral, and cognitive predictors of functional outcomes that are particularly relevant for HIV-infected women.**

The WIHS is in a unique position to examine the relationship between overall and domain-specific cognitive performance measures, and everyday functioning with a focus on relevant gender-related outcomes and HIV disease outcomes in a sociocultural context. Individual, family, and community factors may confer protection from, or risk for, the loss of cognitive and functional abilities required to successfully manage financial/household resources, complex medical treatment, referrals, and polypharmacy, and the practical and emotional challenges associated with family and social role functions (e.g., household burden/stress, parenting/grandparenting efficacy, community involvement). Additionally, significant functional disabilities may arise from pathophysiologic processes associated with aging that may prematurely manifest in the context of HIV infection.

Relatively little is known about the impact of neurocognition on functional outcomes such as caregiving and employment. As the WIHS participants age, many find themselves in the position of having to care for grandchildren or children of other relatives while the parents (usually mothers) of the children complete school or go to work. This expectation is particularly salient among African American older women as there is a cultural norm for childcare to remain within the family. It is unclear how neurocognitive decline associated with HIV (and/or aging) would impact women’s ability to care for children and how the potential stress associated with caregiving within the context of living with a chronic illness might affect these women’s lives. This area is ripe for investigation, given the paucity of literature in this area. The only published studies on cognitive difficulties and parenting focus on the negative impact that intellectual disability has on parenting skills among HIV-uninfected individuals, and these studies generally focus on the functioning of the children of these adults, not the adults themselves. Studies of HIV-positive mothers point to the impact that parenting stress has on outcomes such as adherence, but these studies do not consider the role of neurocognitive functioning in these relationships.

The WIHS core interview has been revised for visit 30 to obtain data on: (1) the burden / support continuum of adults in the participant’s household; (2) the burden / support continuum of children in the participant’s household; (3) parenting/grandparenting self-efficacy; and (4) the employment continuum. Included are annually-administered questions related to adult and child household composition, self-perception of stress level due to childcare and caregiving efficacy, and the extent of physical and emotional support from adult and child members of the participant’s household, and semi-annually-administered questions related to self-assessed employment efficacy, reasons for unemployment, and community involvement.

Impaired neurocognitive functioning among HIV-positive individuals is associated with unemployment. In a small pilot study conducted within the WIHS, findings indicated that increased neurocognitive dysfunction was associated with lower employment levels (Martin, et al., unpublished). However, given some of the gender role expectations of aging women in the cohort, it is unclear to what degree employment is considered a possibility. For example, if older
women are expected to stay home and care for family members’ children, employment may not be a viable option. Further, the benefits given to individuals with HIV/AIDS may attenuate any motivation to consider employment due to the fear of losing benefits once a certain salary is obtained.

We will collect information on functional outcomes relating to: (1) management of financial/household resources including employment; (2) adherence to complex medical treatment plans and polypharmacy; and (3) ability to navigate the practical and emotional challenges associated with family and social role functions. The latter will include brief items (1) assessing stress due to single parenting/grandparenting burden, (2) self-assessment of efficacy in those roles, (3) childcare arrangements, (4) custody status, and (5) both positive and negative community involvement (e.g., volunteerism, criminal behavior). We will also assess the particular individual, family, and community factors (e.g., financial resources, motivation for employment, household composition/burden/stress, neighborhood fear/safety, and quality of social interactions) that may confer protection against loss of cognitive and functional abilities and that may moderate the relationship between cognitive performance and functional outcomes.

5. **AIM 5.1. To understand the etiology of cognitive decline in HIV-infected women.**

Of high priority in WIHS-IV will be the integration of neurocognitive and neuropathy data with data from other WIHS working groups to better understand the etiology of cognitive decline and neuropathy in aging HIV-infected women.

Although there have been significant increases in morbidity-free survival time following the introduction and widespread use of effective antiretroviral therapies in the U.S., optimally-treated HIV infection continues to result in excess morbidity and mortality. This excess might reflect pathophysiologic conditions of aging such as cardiovascular disease, metabolic disorders including diabetes, renal insufficiency, or reactivation of latent infections due to age-related immunosuppression and/or immune activation. Most of the immunologic, metabolic and cardiovascular predictors of interest will not be collected on all WIHS participants at every visit. Therefore, the NCWG plans to propose appropriate methods and designs on a project-by-project basis to investigate these factors in relation to cognitive change. Individual projects such as these will be proposed via the existing concept sheet submission mechanism, in which groups of investigators propose to collaborate on a nested project. The Executive Committee will review each concept sheet. (See *Manual of Operations, Section 3, Publication Policy*, for detailed information regarding the submittal and review of concept sheets to the WIHS.) Here, we aim to recognize the available and evolving range of predictors of interest in order to provide a framework for future individual proposals.

HIV patients demonstrate phenomena associated with premature aging, such as telomere shortening and diminished immunologic repertoire. A range of studies have identified immunologic perturbations that occur in treated HIV infection, indicating that full recovery of immune function does not always occur even with optimal combination antiretroviral therapy. These same immunologic abnormalities occur to some extent in normal aging. Therefore, the lack of immune recovery to pre-infection norms may drive perturbations that resemble aging. Many age-associated conditions, such as cardiovascular disease, are caused by or associated with immunologic activation. Increasingly, the immunologic characteristics that persist in treated HIV patients have been found to be implicated in the pathogenesis of the diseases of aging. Hepatitis C infection is relatively common in the WIHS cohort, and can be an additional cause of immunologic abnormality and brain dysfunction. Thus, the WIHS working groups focused on HIV pathogenesis, cardiovascular disease, cancer, and metabolic issues have independently proposed studying a similar array of immunologic markers to determine which factors precede or are associated with these disease outcomes. These factors include cellular and soluble immunologic and metabolic indicators such as IL-6, IL-13, IL-17, TNF-a, IFN-g, cellular
apoptosis, antigen specific responses, markers of T regs, and measures of HCV morbidity. Many of these immunologic factors are interrelated and have unique advantages and shortcoming in terms of measurement methods. WIHS is currently performing hypothesis-generating pilot studies to identify the immunologic factors that best characterize outcome phenotypes in the cohort. Once pilot work is complete, a validated panel of immunologic measures will be applied to studies of aging phenomena in WIHS. Since cognitive decline in HIV infection may resemble the other conditions of early aging, WIHS has proposed examining the relationship between these measures of immunologic activation and cognition.

An expanding body of evidence links cardiovascular risk factors — including central adiposity, hyperlipidemia, hypertension, and subclinical measures of atherosclerosis, such as carotid intimal medial thickness (CIMT), — with cognitive decline in healthy adults. There have been few studies exploring cardiovascular and metabolic risk factors in HIV-infected adults. One investigation demonstrated greater CIMT in HIV-positive men, with no relationship to cognition. Recent evidence in a largely male sample of HIV patients demonstrated a relationship between insulin resistance and advanced stages of neuropsychological impairment. In collaboration with other working groups, we will propose substudies examining the association between specific cognitive domains and several cardiovascular and metabolic disease risk factors, including modifiable risk factors. Cardiovascular markers of interest include brain-derived natriuretic peptide (BNP), leptins, ankle-to-brachial index, left ventricular mass, CIMT, and hypertension. Metabolic markers of interest include diabetes, insulin resistance, fasting blood sugar, hemoglobin A1c levels, body mass index, and anthropometric measurements. Other predictors of interest include active Hepatitis C infection defined as the presence of Hepatitis C viremia, subject host genetics (e.g., apolipoprotein E genotype), and use of select prescription medications (e.g., interferon, psychotropic medications, other CNS-penetrant drugs).

6. **AIM 5.2. To understand the prevalence and etiology of neuropathy in WIHS women.**

Another primary focus of investigation in WIHS-IV is the prevalence and etiology of neuropathy in HIV. Although at least 14 different neuropathic syndromes are associated with HIV, distal sensory polyneuropathy (DSPN) associated with advanced HIV is the most prevalent. Estimates of prevalence are as high as 30% in patients with severe HIV, with much lower estimates in patients with milder illness. Once again there is less information available on the prevalence and incidence of DSPN in women compared with men, and in mild HIV compared with severe HIV. The same factors that may lead to differences in rates of cognitive impairment between men and women may also be associated with differences in rates of DSPN.

Formal examination of reflexes and vibratory sense, as well as self-report of symptoms, will continue in WIHS-IV. Furthermore, the core interview includes an assessment of clinical symptoms that includes self-report of pain and tingling in arms, legs, hands or feet. Silverberg, et al., examined the prevalence of these symptoms between 2000 and 2004 with respect to HIV infection and the use of HAART in WIHS and found that the prevalence of DSPN in HIV-uninfected women was 9.2%, but was significantly increased in HIV-infected women to 17-25%. HIV-infected women remained at an elevated risk of paresthesias after controlling for age, race/ethnicity, body mass index, category of HIV risk at baseline, and alcohol intake. Additional unpublished recent analyses have estimated the OR (95% CI) for neuropathy associated with HIV infection to be 1.81 (1.33, 2.45), HCV-infection to be 1.75 (1.34, 2.27), and each 10-year increase in age to be 1.32 (1.14, 1.52). These analyses demonstrate that symptoms of neuropathy are prevalent in WIHS and increase with age; however, formal and more objective assessments are needed to know how these symptoms relate to signs of peripheral neuropathy, to determine the prevalence and incidence of neuropathy, and to understand the factors that predict neuropathy. During WIHS-IV we will also link with other cohorts and investigators to investigate sex differences in DSPN and predictors of DSPN.
C. WIHS NEUROCOGNITIVE PROTOCOL FOR ASSESSMENT OF COGNITION AND EDUCATIONAL EXPERIENCE

The Neurocognitive Study will involve additional data collection from all WIHS participants. Neurocognitive tasks will be administered to assess performance in the cognitive domains of: (1) verbal memory; (2) executive function; (3) psychomotor speed; (4) attention/concentration; and (5) fine motor control. If a particular task is not attempted or is attempted but not completed, this should be indicated, along with the reason for non-completion, in the appropriate questions on the form for that task. Assessment of post-traumatic stress disorder symptoms (PTSD), menopausal symptoms (MEN01 and BLSA), reading level (NC02a and NC02b), premorbid intelligence (NC04), and educational experience (NC03) will also be included in analyses for neurocognitive-related aims.

NOTE: Participants should be reminded prior to their visit to bring necessary eyeglasses or hearing aids for completion of these tasks.

1. COGNITIVE MEASURES: STANDARD TRAIL MAKING AND SYMBOL DIGIT MODALITIES TASKS (NC01a and NC01b)

All WIHS women will be invited to perform the Standard Trail Making (TMT) and Symbol Digit Modalities (SDMT) Tasks during visits 21 through 24, and again at 24-month intervals beginning at visit 30. Each participant should be given blank test papers to use to complete the tasks; when completed, the participant’s WIHSID and visit number should be written on each test paper and the test papers should be saved in the participant’s visit records with the completed NC forms.

Any external interruption (e.g., phone, beeper, knocking) during administration of the timed TMT or SDMT will invalidate the testing. If a task is interrupted, the participant is allowed to make one additional attempt to complete another blank test. Interviewers should score the second test and discard the first, incomplete test. Participants are not allowed to attempt any task more than twice.

a. Standard Trail Making Task (NC01a, Section B): Visits 21 through 24; Visits 30+

Parts A and B of the Standard Trail Making Task (TMT) will be administered based on procedures described by Reitan (1985)\(^67\). Part A requires participants to “connect the dots,” i.e., circles marked 1 through 25, with a pencil as quickly as they can, in order. Part B is a more complex sequencing task, requiring shifting between numbers 1 through 13 and letters A through L, i.e., 1 to A to 2 to B, etc. Administration time for the TMT is approximately eight minutes.

b. Symbol Digit Modalities Task (NC01a, Section C): Visits 21 through 24; Visits 30+

The Symbol Digit Modalities Task (SDMT) will be administered based on procedures described by Smith (1982)\(^68\). The SDMT is a measure of mental speed and attention, which involves participants transcribing a series of symbols corresponding to digits (1–9) from a key with their appropriate digits presented. Subsequently, a delayed recall trial requires the participant to match symbols with their corresponding digits without referencing the key. Administration time for the SDMT is approximately three minutes.

c. Color Trail Making Task (NC01b): Visits 21 through 23; DC and LA sites only

The Color Trail Making Task involves connecting circles containing the numbers 1 through 25 in order as quickly as possible; however, in this task the participant must shift between different-colored circles. Interviewers should be careful not to state the colors, but only to demonstrate that there are two different colors. The Color Trails assesses visual attention and psychomotor speed, but also requires a higher level of executive functioning skills.
All participants (both Spanish- and English-speaking) at the DC and LA sites will receive both the Standard TMT and the Color Trails. This will enable conversion of Color Trails scores to Standard TMT scores and comparisons with MACS data. The Color Trails do not require knowledge of the English alphabet.

Administration order of the Standard TMT and Color Trails in DC and LA should alternate to reduce potential bias; meaning that the order in which the Standard TMT versus Color Trails are given should not be the same for all participants. To standardize the order of administration of these tests, all participants whose seventh digit in their WIHSID is even should receive the Standard TMT and then the Color Trails. All participants whose seventh digit in their WIHSID is odd should receive the Color Trails and then the Standard TMT. Interviewers will record on the NC05 form whether NC01a or NC01b was administered first.

2. **READING LEVEL (NC02a and NC02b)**

   a. *English Word List (NC02a)*: One-time administration only at visits 21, 22 or 30+

      English reading level will be measured using the *Reading Recognition subtest from the Wide Range Achievement Test – Version 3 (WRAT-3)*. All WIHS participants (both English- and Spanish-speaking) should be administered this form once. Beginning with visit 30, sites should administer the NC02a to every participant that did not complete it during WIHS-III. English and Spanish versions of the form are provided so that monolingual Spanish speakers understand the instructions needed to complete this test; however, the testing itself will be performed in English only. Participants are asked to name letters and pronounce words out of context. The words are listed in order of decreasing familiarity and increasing phonological complexity. Prior studies show that quality of education, as estimated by WRAT-3 score, is a more powerful predictor of cognitive test performance and cognitive decline than years of education, especially among ethnic minorities. This measure takes between one and two minutes to administer.

   b. *Spanish Word List (NC02b)*: One-time administration only at visits 21–23 or 30+

      Participants who regularly have their interviews conducted in Spanish should be administered the *Word Accentuation Test (WAT)*, which tests Spanish reading level. All Spanish-speaking participants should be administered this form once.

3. **EDUCATIONAL EXPERIENCE (NC03)**: One-time administration only at visits 21, 22 or 31+

   Collection of educational experience variables will be conducted one time only. Beginning with visit 31, sites should administer the NC03 to every participant that did not complete it during WIHS-III, including southern site recruits. The data collected on this form will provide considerable benefits to future analyses, including more accurate interpretation of neurocognitive test scores and powerful prediction of age-related cognitive decline.

   The form provides detailed information about educational attainment and clarification of the setting in which education was completed. The structure of the questionnaire allows for data collection on multiple schools at each level of education. The following variables are assessed separately for elementary, high school, and post-high school phases of education: years completed, age or date of first year attended, location (e.g., country, state, city, rural versus urban), setting (e.g., public versus private, one-room school or multi-room school), and estimated ethnic composition of student body and faculty.
4. PREMORBID INTELLIGENCE (WTAR) (NC04): One-time administration only at visits 22, 23 or 30+

Premorbid intelligence will be measured using the Wechsler Test of Adult Reading (WTAR). All English-speaking WIHS participants should be administered this form once. Beginning with visit 30, sites should administer the NC04 to every participant that did not complete it during WIHS-III.

The test is composed of a list of 50 words that all have atypical grapheme to phoneme translations. The intent in including words with irregular pronunciations is to minimize the current ability of the participant to apply standard pronunciation rules and to assess previous learning of the word. The WTAR was developed and co-normed simultaneously with the widely used WAIS–III and WMS–III. Therefore, scores on the WTAR can be used to estimate full scale IQ, verbal IQ, and performance IQ scores based on demographic characteristics (e.g., age, education, sex, and ethnicity).

5. HOPKINS VERBAL LEARNING TEST-REVISED (HVLT-R) (NC06): Visits 25 and 30+

All WIHS women will be invited to perform the Hopkins Verbal Learning Test-Revised (HVLT-R) during visit 25, and again at 24-month intervals beginning at visit 30. The HVLT-R is a measure of verbal learning and memory and will be administered based on procedures specified by Brandt & Benedict (2001)\textsuperscript{65}. The test consists of a list of 12 words (HVLT-R Word List) from three taxonomic categories, which are read aloud to the participant. The Immediate Recall trials include three learning trials. Delayed Recall and Recognition are assessed 20 to 25 minutes after completion of the Immediate Recall trials. Administration time is approximately seven minutes for the Immediate Recall trials and approximately three minutes for the Delayed Recall and Recognition trials.

The HVLT-R Form 1 was administered during visit 25 and visits 30 through 33 (wave 1). The HVLT-R Form 3 was administered during visits 34 through 37 (wave 2). The HVLT-R Form 4 was administered during visits 38 through 41 (wave 3). The HVLT-R Form 5 was administered during visits 42 through 45 (wave 4). The HVLT-R Form 6 will be administered during visits 46 through 49 (wave 5.)

6. THE STROOP TASK (NC07): Visits 25 and 30+

All WIHS women will be invited to perform the Stroop Task during visit 25, and again at 24-month intervals beginning at visit 30. The Stroop Test will be administered based on procedures described by Comalli (1962)\textsuperscript{66}. The test consists of three trials: (1) The Color Naming Trial and (2) The Word Reading Trial measure attention and concentration; (3) The Interference Trial is a measure of divided attention and inhibition that takes advantage of people’s ability to read words more quickly and automatically than they can name colors. Administration time for all three trials is approximately eight minutes.

7. VERBAL FLUENCY (NC08): Visits 30+

All WIHS women will be invited to perform the Verbal Fluency Task at 24-month intervals beginning at visit 30. Verbal fluency requires the production of words within a time limit and under a specific constraint, e.g., words beginning with the letter “F” (Letter Fluency) or names of animals (Semantic Fluency). This is an executive function task where strategies such as clustering can be implemented in order to facilitate word production. The Verbal Fluency Task consists of Letter and Semantic Fluency Tasks. The Letter Fluency Task includes three one-minute trials using the letters F, A, and S. The Semantic Fluency Task is a one-minute trial using the category animals. Administration time for the Verbal Fluency Task is approximately five minutes.
8. LETTER-NUMBER SEQUENCING TASK (LNS) (NC09): Visits 30+

All WIHS women will be invited to perform the Letter-Number Sequencing Task at 24-month intervals beginning at visit 30. The LNS is a standardized executive function task used to assess verbal working memory performance. In the Experimental Condition, participants are read a series of letters and numbers and asked to recite both back in ascending order, with the numbers first and then the letters. The test involves a 24-item Experimental Condition followed by a Control Condition, in which participants simply repeat back the sequence of letters and numbers in the order presented. Administration time for the LNS is approximately seven minutes.

9. GROOVED PEGBOARD (NC10): Visits 30+

All WIHS women will be invited to perform the Grooved Pegboard Task at 24-month intervals beginning at visit 30. The Grooved Pegboard is a manipulative dexterity task measuring visual-motor coordination. The testing equipment consists of a pegboard with 25 holes with randomly positioned slots, and pegs with a key along one side. The participant is to insert the pegs as quickly as possible into the pegboard slots, in sequence, first with the dominant hand and then with the non-dominant hand. Test duration is approximately five minutes. The Grooved Pegboard is the only task in the battery that requires equipment (pegboard and pegs) other than a stopwatch, test forms, and pencils.

D. TIMEFRAME

1. WIHS-IV NEUROCOGNITIVE BATTERY: VISITS 30 THROUGH 45

The WIHS-IV Neurocognitive (NC) Battery will be administered during WIHS-IV and WIHS-V at 24-month intervals with test administration beginning at visit 30 and 25% of the cohort being tested during each visit cycle. Baseline NC Battery administration will take place during visits 30 through 33 (wave 1); first follow-up administration will take place during visits 34 through 37 (wave 2); second follow-up administration will take place during visits 38 through 41 (wave 3); third follow-up administration will take place during visits 42 through 45 (wave 4). Participants with a history of missed visits should be asked to complete the NC Battery during the first opportunity that they attend a WIHS visit during the baseline cycle of the battery (i.e., their first appearance at visits 30 through 33). If a participant does not complete the NC Battery during wave 1 (visits 30 through 33), she should still be asked to participate in testing during a later wave.

Administration time for the entire NC Battery is estimated to be 60 minutes. The NC Battery should be administered in the order listed below:

a. Neurocognitive Study Introduction (Appendix B)

b. IADL, Lawton Instrumental Activities of Daily Living
   a. IADL-LF, long form – for first administration
   b. IADL-SF, short form – for subsequent administrations

c. NC06, Section B, Hopkins Verbal Learning Task-Revised (HVLT-R) – Immediate Recall trials

d. NC07, Stroop Task

e. NC01a, Section B, Cognitive Measures – Standard Trail Making Task

f. NC01a, Section C, Cognitive Measures – Symbol Digit Modalities Task

g. NC06, Section C, Hopkins Verbal Learning Test-Revised (HVLT-R) – Delayed Recall and Recognition trials. The Delayed Recall and Recognition trials must be administered 20 to 25 minutes after completion of the HVLT-R Immediate Recall trials.
h. **NC08**, *Verbal Fluency Task*

i. **NC09**, *Letter-Number Sequencing Task (LNS)*

j. **NC10**, *Grooved Pegboard*

k. **NC02a**, *English Word List (WRAT-3)* – Administer only to participants (including both monolingual and bilingual Spanish speakers) who did not complete the task during WIHS-III, including southern site recruits. Although the test will always be conducted in English, the **NC02a** Spanish version has a Spanish translation of the task instructions and should be administered to women who prefer their testing be conducted in Spanish to ensure their understanding of the task requirements.

l. **NC02b**, *Spanish Word List (WAT)* – Administer only to participants who did not complete this task in WIHS-III, including southern site recruits. Administer to Spanish-speakers only.

m. **NC04**, *Pronunciation Word List (WTAR)* – Administer only to participants who did not complete this task in WIHS-III, including southern site recruits. Participants that speak and read English fluently on a regular basis are eligible to complete this task.

n. **NC03**, *Educational Experience* – Administer only to participants (including both monolingual and bilingual Spanish speakers) who did not complete the task during WIHS-III, including southern site recruits. Beginning with visit 31, this form will be administered at the end of the core interview, not during administration of the NC Battery.

O. **PTSD**, *Stress Assessment Questionnaire*

p. *Neurocognitive Study Closing Statement (Appendix C)*

**NOTE:** The above-listed NC Battery is for administration to English-speaking participants only, save for noted exceptions of **NC02a** and **NC02b**.

**NOTE:** During wave 1 of the NC Battery, the **PTSD** form was administered first. During wave 2 of the NC Battery, the **PTSD** was moved to the end of the battery so that feelings brought up during administration of the questionnaire would not interfere with participants completing the other NC tasks.

2. **WIHS-III NEUROCOGNITIVE BATTERY: VISITS 21–24**

   a. **NC01a**, *Standard Trail Making Task and Symbol Digit Modalities Task* – Administered after *F22HX* to all participants at visits 21–24

   b. **NC01b**, *Color Trail Making Task* – Administered after *F22HX* to DC and LA participants only, at visits 21–23

   c. **NC02a**, *English Word List* – Administered after *F24* to English-speaking participants only, at visit 21

   d. **NC02b**, *Spanish Word List* – Administered after *F24* to Spanish-speaking participants only, at visit 21

   e. **NC03**, *Educational Experience* – Administered after **NC02a/NC02b** to all participants at visit 21

   f. **NC04**, *Pronunciation Word List* – Administered after *F24* to English-speaking participants only, at visit 22
g. **NC05, Interviewer Feedback** – Completed by interviewers after completion of NC testing to record any issues encountered during administration of WIHS-III NC Battery

### E. ADMINISTRATION AND SCORING GUIDELINES

1. **INFORMED CONSENT**

Sites must obtain informed consent for the NC Battery prior to beginning testing. Information regarding administration of the NC Battery can be included either in the core WIHS consent form, or in a separate consent form specifically for the Neurocognitive Study. Suggested language for the consent form includes:

- **Purpose:** The purpose of this [consent form / signature page] is to inform you of new questions that are being added to your routine WIHS visit and to obtain your consent for administration of these questions.

- **Procedures:** Beginning with this visit, the WIHS will add new interview questions related to education and literacy, and will ask you to perform selected cognitive tasks, as part of your routine WIHS visit once every two years. The purpose of this testing is to look at the effects of aging and of the medications used to treat HIV on your mental function over time. You will be asked about your educational experience and will be asked to read words of varying difficulty to assess your reading skills. You will also be administered a series of mental tasks that will require the use of visual perception, problem solving, memory and other cognitive functions. Each of the tasks will be administered either verbally or in a paper-and-pencil format. We expect the addition of these tasks will add about 60 minutes to your WIHS interview once every two years.

- **Risks:** Your participation involves the following risks: (1) You might feel uncomfortable or embarrassed when discussing your educational experience. However, everything possible will be done to minimize the discomfort you may feel answering these questions, and you may make comments or ask the interviewer questions at any time. If you wish, you can refuse to answer any question you are asked. (2) Participation may lead to fatigue, boredom, or frustration, since some of the tasks may be difficult. If at any point during the evaluation you find it difficult to continue, you can take a rest break. (3) It is important to understand that the results of these tasks are not meaningful without a complete neurocognitive assessment. These tasks are not a substitute for a full evaluation of neurological and/or cognitive function. If you have specific concerns about your memory or other cognitive abilities, we can provide you with the names of centers that do these evaluations or you can discuss this with your health care provider.

- **Compensation:** If you complete all the tasks in the Neurocognitive Battery, you will receive compensation of 25 dollars in addition to what you already receive for attending your WIHS core visit.

- **Cost:** There is no cost to you for participation in this study.

- **Confidentiality:** Results of these tasks will be part of your WIHS record. However, there are no names to identify you on any of these questions or tasks because participants are identified by study number only. The link between your name and your study number will continue to be kept in a separate locked file in the WIHS office and will not be shared with researchers.

- **Consent to Participate:** I have read and understand the purpose of these new questions and tasks for the WIHS or this has been read to me by _________________. Anything I did not understand was explained and all my questions were answered to my satisfaction. I agree to participate in this research. I acknowledge that I have received a personal copy of this consent form.
2. FOLLOW-UP VISIT SEQUENCE WITH NEUROCOGNITIVE BATTERY

The entire follow-up visit with NC Battery is to be administered during a single appointment. Sites should make every attempt to follow the order described below, keeping in mind that deviation from the protocol should be kept to the absolute minimum. All exceptions should be fully documented by writing a memo to the Data Manager and Project Director citing the participant’s WIHSID and an explanation of what happened. This memo should be copied to the participant's study files.

a. Phlebotomy, Urine Collection

- **Phlebotomy**: Phlebotomy should be performed at the start of the participant’s visit. All participants who attend their WIHS visit after having fasted for eight hours should be offered a small snack and drink before being asked to proceed with the rest of their visit.
- **Urine Collection**: One urine specimen must be collected during the follow-up visit. It is recommended that collection occur prior to the gynecological exam.

b. Neurocognitive Battery

The entire battery (as listed in **Section D**) should be administered in that order, at one time, by a single, certified interviewer, immediately following phlebotomy and consumption of a snack by the participant. This should be at the beginning of the visit before any of the core interviews or examinations (physical or gynecological) have been administered. This will ensure that women completing the NC Battery are well-rested, not hungry or thirsty, and in top mental condition for the testing.

c. Physical Exam and Core Interview

The site can choose in what order to administer the physical exam and core interview. Either can be done first.

The **physical exam** includes the ABI, neuropathy and gynecological exams.

The entire core interview (as listed in **MOO, Section 7**) should be administered in that order, at one time, by a single interviewer. If the exam is performed before the core interview, ensure that the participant receives clear instruction during the interview to not include any diagnoses found during her physical exam at this core visit. Only diagnoses since her last study visit should be reported.

d. Substudy Forms

All site-specific substudy forms that are not part of the WIHS NC Battery or core interview should be administered after completion of all core interview forms.

e. Colposcopy

According to the colposcopy protocol (See **MOO, Section 9**), sites will perform colposcopies as clinically indicated after the gynecological exam has been completed.

3. STANDARD INTRODUCTORY AND CLOSING STATEMENTS

Interviewers should read the Neurocognitive Study Introduction to the participant, located in **Appendix B**, before beginning administration of the Neurocognitive Battery. Subsequent to completion of the NC Battery, interviewers should read the Neurocognitive Study Closing Statement to the participant, located in **Appendix C**.
4. GENERAL INSTRUCTIONS

The WIHS NC Battery is a brief battery designed to assess cognitive impairment. The instructions given for administration are intended to ensure standardized administration of the tasks among all interviewers in order to maintain inter-rater reliability. Therefore, it is important to use only the instructions and cues described in the Manual of Operations, form scripts and QxQs when administering these instruments. Additional hints, cues, or strategies should not be given because they can influence a participant’s score and bias results. Interviewers should always refer to the NC Battery components as “tasks,” and not “tests,” when speaking to participants.

Do not tell the participant the time limit for any of the tasks she is performing. For paper-and-pencil tasks, if a task is interrupted, the participant can make one additional attempt on a new test page. Interviewers should score the second test page and discard the first, incomplete test page. Participants may not attempt any task more than twice at a single visit.

Several general rules should be kept in mind when administering and scoring the NC Battery:

a. All responses should be recorded exactly as given.

b. It is better for a participant to give an incorrect response than to give no response at all; therefore, participants should be gently encouraged to try each task even if they are unsure, as an incorrect response can give some evidence that the subject at least understood the task. “Give it your best try,” or, “It is okay if you're not sure,” can be helpful prompts. If a participant asks for help while completing a task, say, “I want to see how well you can do it yourself.”

The Neurocognitive Study Introduction (Appendix B) will be read prior to beginning the assessment in order to let participants know the purpose of the testing and how the scores will be used. The introduction also reassures participants that they will likely find some tasks difficult because they are designed to be difficult; participants should remember to give their best effort.

c. Scoring should follow the rules described in the Manual of Operations, form scripts and QxQs, and should agree with the approved interviewer training materials. Interviewers should use a different colored pen or pencil than the participant when making interventions and scoring marks during completion of pencil-and-paper tasks.

d. Assessment is most useful when optimum performance is elicited. Within the rules for standard administration, interviewers should attempt to ensure the participant understands what each task demands and has the opportunity to respond in order to elicit a valid measure.

e. An interviewer’s main tools are a stopwatch (“beepless” preferred), scoring sheet, and a pen or pencil. The Grooved Pegboard test requires a pegboard and pegs. Instructions for each of the tasks should be read verbatim; it is acceptable to read them off of the form if they are not memorized. Approved cheat sheets with instructions and probes can and should be used during training and initial administration of the NC Battery to participants.

f. Seating arrangements for the testing are important. Ideally, the tester should sit directly across from the participant at a table or desk that allows the participant’s legs to fit underneath. If the tabletop is rough, a smooth surface should be placed on the table such as a large clipboard or pad of paper. The height of the desk or table should allow the participant to work comfortably.

g. Testing should occur in a well-lit, ventilated, quiet interview room with seating as close to the “ideal” as possible. Only the interviewer and the participant should be present. An observer is allowed to be present during yearly interviewer evaluations and site visits. Noise should be minimized by: (1) hanging a “Quiet: Testing in progress” sign on the door to eliminate
interruptions and noise right outside the room; (2) turning off phone ringers and pagers in the room; and (3) choosing a room that is quiet and insulated from external noise, if possible.

5. STANDARD TRAIL-MAKING TASK (NC01a, Section B) ADMINISTRATION GUIDELINES

The interviewer who administers the Standard Trail Making Task, Parts A and B, should also score the tasks. The score is based upon (1) the times to complete each part of the task, (2) the number of interviewer prompts, (3) the number of participant errors, and (4) the number of correctly connected points. The NC01a Scoring Form can be completed while the participant is undergoing her WIHS examinations or after she has completed her entire core visit.

a. **Timing**

Timing should begin as soon as the interviewer says, “Begin!” or “Go!” and end as soon as the tip of the participant’s pencil reaches the circle marked “END.” Time to complete the tasks is recorded in minutes and seconds. Participants should be allowed a maximum of five minutes to complete each task. In order to maintain rapport with the respondent, the interviewer may choose to either stop the participant after five minutes has elapsed, or allow her to finish the trial. The practice portions of Parts A and B are not timed.

b. **Prompts**

A prompt is an instance in which the interviewer has to redirect the participant after an error. Up to 10 seconds are allowed for the participant to make a connection between one circle and the next. After 10 seconds have elapsed since the last correct response, the interviewer should prompt the participant for the location of the next correct circle by pointing to it. Interviewers should count the number of prompts given during each task.

c. **Errors**

Errors represent the number of times the participant connects to a circle that is not in the proper numerical or alphabetical sequence (e.g., connecting circle 4 to circle 6, skipping circle 5). Interviewers should immediately correct these errors by instructing the participant to return the pencil to the last correct circle and to proceed from there.

6. SYMBOL DIGIT MODALITIES TASK (NC01a, Section C) ADMINISTRATION GUIDELINES

The interviewer who administers the Symbol Digit Modalities Task (SDMT) should also score the task. The SDMT score is the number of correct answers given by the participant in 90 seconds, not including the 10 practice answers, which are untimed. This score is recorded as a proportion of the total number of responses. For example, a score of “20/25” indicates that the participant made a total of 25 responses, with 20 correct and 5 incorrect.

The total number of correct responses can be found by placing the scoring key over the test form and counting the number of correct responses. The total score provides a measure of the speed and accuracy of symbol-digit substitutions.

The delayed recall final score is the number of correct responses on the last line, with a maximum of nine points. There are 15 boxes on the last line; however, four symbols are repeated. Cover the completed test and key, or use a blank paper without the key, and ask the participant to fill in all of the numbers she can remember that go with the symbols on the last line, one after another. Allow the participant the opportunity to complete all 15 boxes, without being timed, and ask her to tell you when she is finished. Record one point for each correct response, not including duplicates. If one of the duplicated symbols is correct and one is incorrect, count this as one point.
7. COLOR TRAILS TASK (NC01b) ADMINISTRATION GUIDELINES

For both Parts 1 and 2, begin timing as soon as you detect movement toward the first circle, and stop timing as soon as the participant’s pencil first touches the outer part of the last circle.

The score is based upon (1) the times to complete each part, (2) the number of interviewer prompts, (3) the number of participant errors, and (4) the number of correctly connected points. Timing, prompts, and errors are defined the same as in the Standard TMT for the Color Trails.

Color Trails errors represent the number of times the respondent connects to a circle that is not in the proper color sequence, irrespective of the number sequence (e.g., consecutively connecting two pink circles or two yellow circles). Immediately correct these errors by instructing the respondent to return the pencil to the last correct circle and to proceed from there.

8. WRAT-3, ENGLISH WORD LIST (NC02a) ADMINISTRATION GUIDELINES

The Wide Range Achievement Test will be administered to both English- and Spanish-speaking participants to assess English reading level. Participants should be given the appropriate response card, from which they will read a list of single words. The words must be pronounced correctly out of context (not within a reading passage).

As the participant reads each word, circle “1” next to the words that are pronounced correctly, and circle “0” next to the words that are pronounced incorrectly. Stop the participant and end the test when she cannot pronounce 10 consecutive words or when she finishes the list. If the participant mispronounces one of the first five words (i.e., see, red, milk, was, then), ask her to read the 15 letters in the letter reading section after completing the word list. The total score is the number of correctly pronounced words and letters out of a total of 57.

9. WAT, WORD ACCENTUATION TEST (NC02b) ADMINISTRATION GUIDELINES

The Word Accentuation Test is designed to assess reading level among Spanish-speaking participants. It assesses familiarity with infrequently-used, irregular Spanish words, and thus measures reading recognition in the same way as the WRAT-3 among English-speakers. The words in the test are irregular, infrequently used, and not contained within a reading passage so that correct pronunciation depends on prior familiarity with the words. Each participant should attempt to read all 30 words. The total score is the number of correctly pronounced words out of a total of 30.

10. EDUCATIONAL EXPERIENCE (NC03) ADMINISTRATION GUIDELINES

The Educational Experience Questionnaire collects detailed information about educational attainment and the settings in which education was completed. Interviewers should obtain the same information about each school at the primary, secondary, and post-secondary school levels.

11. WTAR, WECHSLER TEST OF ADULT READING (NC04) ADMINISTRATION GUIDELINES

The Wechsler Test of Adult Reading (WTAR) is designed to assess premorbid intelligence levels among English-speaking participants. As the participant reads each word, circle “1” next to the words that are pronounced correctly, and circle “0” next to the words that are pronounced incorrectly. Acceptable pronunciations, including alternate pronunciations, are provided on the NC04 Scoring Form. The participant is required to give only one pronunciation of a word. Participants should attempt to read all 50 words. The total score is the number of correctly pronounced words out of a total of 50.
12. INTERVIEWER FEEDBACK (NC05) COMPLETION GUIDELINES

The Interviewer Feedback (NC05) form was completed by interviewers at each visit, for each participant to whom any component of the NC Battery was administered during WIHS-III. The NC05 is used to track administration of the NC Battery and compliance with the protocol. Interviewers should be as descriptive as possible in responding to open-ended questions to assist in determining how these measures are being received in the field.

13. HOPKINS VERBAL LEARNING TASK-REVISED (HVLT-R) (NC06) ADMINISTRATION GUIDELINES

The scores for the Immediate and Delayed Recall trials are based upon the number of intrusions, clusters and correct responses (i.e., words recited from the HVLT-R Word List). These outcome measures are calculated by the interviewer for each of the three Immediate Recall trials and the Delayed Recall trial. The NC06 Scoring Form can be completed while the participant is undergoing her WIHS examinations or after she has completed her entire core visit.

a. **Number of Correct Responses**

For each of the three Immediate Recall trials and the Delayed Recall trial, compare the words recited by the participant (recorded on the HVLT-R Worksheet) to the HVLT-R Word List on page 1 of the form. Circle “1” for each word from the HVLT-R Word List that the participant remembers and recites back to you, and “0” for each word she does not remember. Do not leave any questions blank.

b. **Intrusions**

An intrusion is a word recited by the participant that is not included in the HVLT-R Word List on page 1 of the form. For example, “book” is not included in the HVLT-R Word List, so if recited by the participant, it would be counted as an intrusion. Each unique word recited that was not on the HVLT-R Word List should be counted as an intrusion; however, if the same intrusion is recited multiple times, it should count as only one intrusion.

c. **Clusters**

A cluster is when the participant recites any two or more semantically-related words in sequence. The words included in the HVLT-R Word List are divided into three semantic categories. If a participant recites any two or more of the words from one category in sequence, this would be counted as a cluster.

The forced-choice Recognition trial is scored during administration. Circle “1” for each word the participant indicates is on the HVLT-R Word List, and circle “0” for each word the participant indicates is not on the HVLT-R Word List.

14. STROOP TASK (NC07) ADMINISTRATION GUIDELINES

The interviewer who administers the Stroop Task should also score the task. The score is based upon (1) the times to complete each part of the task, and (2) the number of participant errors made on each trial.

a. **Timing**

Timing should begin as soon as the interviewer says, “Begin!” or “Go!” and end as soon as the participant recites the last word or color on the response card for the specified task. Time to complete each task is recorded in minutes and seconds. Participants should be allowed a maximum of four minutes to complete each trial. In order to maintain rapport with the participant, the interviewer may choose to either stop the participant after four minutes or allow the participant to finish the trial. The practice rows for each trial are not timed or scored for errors.
b. **Errors**

When the participant makes an error, circle the word on the form script. Draw a single line through any mistake that the participant notices and corrects on her own. Errors are only those mistakes that the participant does not correct spontaneously. The total number of errors per trial should equal the number of circled words without a line through them.

15. **VERBAL FLUENCY TASK (NC08) ADMINISTRATION GUIDELINES**

The score for the *Verbal Fluency Task (NC08)* is based upon the number of correct responses, intrusions and perseverations for each letter or semantic category. The *NC08 Scoring Form* can be completed while the participant is undergoing her WIHS examinations or after she has completed her entire core visit.

1) **LETTER FLUENCY TASK**

a. **Correct Responses**

Any English word that begins with the appropriate letter and has not been said already within a trial is counted correct, except for proper names (e.g., Barbara, Baltimore, Spanish) and words with minor variations in the ending. If the participant gives the same word with different endings (e.g., run, runs, running, ran; eat, eaten, ate; frog, frogs), only count the first word and not the subsequent words. This rule applies only to suffixes that change the tense of a verb or change a word from singular to plural, but do not significantly alter the meaning of the word (e.g., say, said; fix, fixed, fixing; apple, apples).

- This rule does not apply to words with a common root but different meanings (e.g., art, artful, artisan, artless; further, furthermore; help, helpful; fool, foolish, foolhardy; sun, sunny, sunshine; friend, friendly). Each of these words should be counted as an individual correct response.
- This rule also does not apply to words that change pronunciation (e.g., mouse, mice; person, people) when being made plural. Each of these words should be counted as an individual correct response.
- Numbers are allowed. However, if the participant says, for example, “50, 51, 52…,” she will get credit for “50” but not for additional numbers within a series (e.g., 51 and after).
- Slang terms (e.g., sis; ain’t) and foreign words (e.g., faux pas; sauté) are permissible as long as they can be found in a standard English dictionary.
- Words that refer to the same position but with a different gender are permissible (e.g., actor, actress).

b. **Intrusions**

An intrusion is a word that does not start with the given letter, is not an English word, or is a proper name (e.g., Japan, Amish, Susan).

c. **Perseverations**

A perseveration occurs when the exact same word is produced more than once within a trial. Only the first time that the word is said should be counted. Remaining instances are scored as perseverations.

- Words with different endings are not counted as perseverations even though they are not counted as correct responses. A word must be exactly the same as a previously produced word in order to be considered a perseveration.
• If a word is given twice but has two potential different spellings (e.g., forth, fourth), the participant should get credit for both spellings. Always give the participant the benefit of the doubt.

2) SEMANTIC FLUENCY TASK
   a. Correct Responses
      Any word produced by the participant in the category of animal (including insects, birds, man, etc.) is counted. If the participant gives a superordinate category (e.g., monkeys) and also gives exemplars of the category (e.g., gorillas, chimpanzees), she should get credit for naming all three of the animals. Names of extinct or imaginary animals (e.g., unicorn, dragon) are permissible.
   b. Intrusions
      An intrusion is a response that does not fall under the category of animals.
   c. Perseverations
      A perseveration occurs when the same animal is said more than once within a trial. Only the first time that an animal is said should be counted. Remaining instances are scored as perseverations.

16. LETTER NUMBER SEQUENCING TASK (NC09) ADMINISTRATION GUIDELINES
   The Letter Number Sequencing Task (NC09) score is based upon the total number of items correct and the longest item passed for each of two conditions (Control and Experimental). The NC09 Scoring Form can be completed while the participant is undergoing her WIHS examinations or after she has completed her entire core visit.
   a. Items Correct
      All responses should be recorded on the line under each item. If the participant gives the wrong sequence, circle the item. A participant may correct herself if the interviewer has not yet moved on to the next item. If the participant self-corrects, draw a line through the circle. Errors are only those mistakes that the participant does not correct spontaneously. This score is called “LNS total” in the Experimental Condition and “LNS Control total” in the Control Condition. The LNS total and LNS Control total should each equal the number of items in their section that are not circled or those that have a circle with a line through it. Practice items are not included in scoring.
   b. Longest Item Passed
      This is the number of symbols (numbers and letters) in the longest item sequence that the participant got correct. This score is called “LNS Sequencing” in the Experimental Condition and “LNS Control Sequencing” in the Control Condition.

17. GROOVED PEGBOARD (NC10) ADMINISTRATION GUIDELINES
   The Grooved Pegboard Task (NC10) score is based upon (1) the time to complete each trial and (2) the number of drops the participant makes during each trial.
   a. Timing
      Start your timer as soon as you tell the participant to begin. Once the participant has placed the last peg in the last hole, stop the timer and record the task duration in minutes and seconds. Participants should be allowed a maximum of five minutes to complete each trial. In order to maintain rapport with the participant, the interviewer may choose to either stop the respondent after five minutes or allow the respondent to finish the trial.
b. **Drops**

A drop should be counted anytime the participant has picked up a peg and then drops it outside of the circular peg holder. If a peg is dropped, the participant should continue with the task, as there are extra pegs available. A dropped peg should not be picked up until after the trial unless it is interfering with administration of the task. If the participant runs out of pegs, a correctly placed peg can be taken out and used again. If the participant accidentally knocks a peg out after placing it in the hole, it is not counted as a drop. If the participant doesn’t drop any pegs, score “Drops” as “00.”

18. MAINTAINING RAPPORT AND REQUESTS FOR RESULTS

Throughout the testing, convey your enthusiasm and interest in what the participant is doing. Praise and encourage the participant for her effort on the tasks. Do not, however, give feedback on whether a specific response is right or wrong, except when instructed to do so using prompts or during the practice items. For example, do not say, “Good,” or, “That was right,” when correct connections are made on the Trail Making Tasks or when symbols are entered correctly on the Symbol Digit Modalities Task after the example items. If a participant has done very poorly on a task and is aware of it, say, “That was a hard one, let's try something else,” and go on to the next task or section.

Many participants will ask for scores or feedback regarding their performance. There is no way for interviewers to determine whether there is clear impairment using these cognitive measures, since (1) there are many reasons why a participant might score poorly, (2) the normative performance in this population is not yet known, and (3) corrections for age, years of education, and other background variables need to be made before interpreting the scores. Results will be calculated during analysis and available in the summary distributions of cleaned and edited data. Results are not clinically evident of cognitive disorders; therefore, referrals should not be made on the basis of performance on these tests alone.

If a participant asks for feedback, say, “You clearly gave your best effort on these tasks and that is great. I can’t give you specific feedback about your score because we need to test everyone in the study a few times before we can interpret what individual scores mean in terms of cognitive performance.”

If a participant expresses significant concern about her cognitive functioning or if it is clear to the examiner that a referral should be made regarding cognitive function, the interviewer or social worker associated with the study should, in consultation with the participant, make a referral to a local memory disorders center or neurologist.

F. TRAINING AND CERTIFICATION

Research personnel that were involved in the pilot studies will lead face-to-face training sessions for test administrators at all WIHS sites. Training sessions include a description of tasks, a review of administration instructions and scoring, viewing task administration by experienced testers on a WIHS training video, supervised mock administration and scoring sessions, and question and answer sessions.

Following the face-to-face training session, interviewers should review training materials and practice test administration. After gaining confidence in their test administration skills, interviewers will submit two audio-taped administrations of the test battery and all forms and test pages used during administration for centralized review. The training staff will review and individually score each neurocognitive task on both tapes. Certification will occur on a task-by-task basis if the interviewers meet task-specific scoring criteria. A scoring checklist was developed for each task by the training staff that designates specific task components that require scoring and the maximum point value for that component. These specific task components vary by task, but include things such as task timing, recording start and end times, answering the task completion questions, recording of participant
responses, and scoring. Each administration of a task will be scored separately using a point value of 0 to 10. In order to satisfy certification requirements, the administrator must have scored at least a 9 on one of the tapes, and a score no less than 6 on the other tape.

Pronunciations of words included on the NC02a, NC02b and NC04 are included on the WIHS Administrative web site: http://statepiaps.jhsph.edu/wihs/admin/pronunciations/pronunciations.html#NC. In addition, a copy of the WIHS training video is located on the WIHS Admin web site: http://statepiaps.jhsph.edu/wihs/admin/interviewer-training/interviewer-training.htm.

A Testing Critiques document is sent to interviewers that indicates for which tasks they were and were not certified and provides detailed written feedback on a task-by-task basis regardless of certification status. The interviewer is asked to carefully review the feedback and practice tasks before resubmitting two audiotaped administrations for the non-certified tasks and all relevant test pages for follow-up centralized review. Interviewers will be asked to repeat this process until all nine tasks in the NC battery are certified.

After certification procedures, the first 10 administrations of the WIHS-IV Neurocognitive battery by each interviewer must be evaluated by the training staff. To do this, please fax original forms and participant test pages for the first 10 administrations of the NC Battery by each interviewer to Jessica Oakley for review (email joakley@psych.uic.edu; fax # 312-413-4265). The training staff will review these 10 administrations and provide feedback to the interviewer via email. At the end of visit 30, sites should send the remaining test forms for the HVLT-R and Verbal Fluency Tasks only in bulk, either electronically as a scanned PDF or via FEDEX to the address listed on the Neurocognitive Testing Checklist.

To increase the reliability of the testing procedures, all certified interviewers will be required to recertify by submitting an audio-taped administration, forms, and test pages every six months for the first year and annually thereafter. The first recertification process will occur six months following the submission of each interviewer’s tenth NC battery administration to the training staff.

G. DATA TRANSMISSION TO WDMAC

If the participant completes any of the NC Battery tasks, then all NC Battery forms should be completed, with the reason any individual tasks were not completed noted on the appropriate form. If the ENTIRE NC Battery was not completed, then the interviewer should complete form NC05, indicating the reason the entire NC Battery was not done. In this case, no other NC Battery forms need be completed.

Forms will be entered into the Apollo data management system. These data will be edited, cleaned, and incorporated into the WIHS database after each semi-annual visit. Please see Section 11 of the Manual of Operations for the scheduled dates of future data releases by visit number.

H. REFERENCES


NEUROCOGNITIVE BATTERY CHECKLIST

BEFORE PARTICIPANT’S VISIT:

☐ Establish whether or not the participant will be receiving the Neurocognitive (NC) Battery according to the following rules:

- Starting at visit 30, the Neurocognitive Battery should be administered to participants at 24-month intervals, with 25% of the cohort testing during each visit window. Testing will not be done for Spanish-speaking participants (except for NC02a and NC02b), so only English-speaking participants should be administered the NC Battery.

- Participants with a history of missed visits should be prioritized for testing at the first opportunity they present during the biannual baseline cycle (i.e., v30–v33). The WIHSID-specific Visit Control Sheet (VCS) will indicate which participants have missed a visit. If a participant does not present during visits 30 through 33, administer her baseline NC Battery during a later wave of WIHS NC testing.

☐ Prepare (and contact the participant in advance, if applicable) for an extra 30 to 40 minutes to be added to the usual WIHS visit duration.

☐ Remind (via usual mechanism – mailing or phone) participants to bring necessary aides, including reading glasses or hearing aids, to their NC visit. Sites should have available spare reading glasses (e.g., from a drugstore) in case a participant forgets to bring hers.

☐ Review the list of participants missing WRAT-3 (NC02a), WAT (NC02b), or WTAR (NC04) forms to find out if these tests need to be given. The WIHSID-specific Visit Control Sheet will indicate whether these are required.

☐ Testing should take place in a quiet, private room that has a desk or other hard, flat surface that can be used by the participant. For paper and pencil tasks, the participant should be provided with a sharp pencil without an eraser; the interviewer should use a different color pen/pencil for making corrections and scoring.

AT THE BEGINNING OF PARTICIPANT’S NEUROCOGNITIVE TESTING:

☐ Ensure the participant has not smoked within 15 minutes of beginning the NC Battery.

☐ Ensure participant’s blood has been drawn and, if fasting, ensure she received food and a beverage. NC testing MUST take place immediately following phlebotomy and refreshment, and prior to the remainder of the visit (i.e., exams, core interview).

☐ Give the participant an opportunity to use the bathroom before testing begins.

☐ Determine whether the current signed participant consent includes the NC Battery. If not, obtain informed consent.

☐ Read the NC Battery Introductory Script (MOO, Section 32, Appendix B) to the participant.

☐ Attempt to administer all tasks to the participant unless she is unable to complete them (e.g., if participant is blind she would not be able to complete the Stroop).
DURING NEUROCOGNITIVE TESTING:

Give the following tests and questionnaires in the order specified below:

☐ Lawton Instrumental Activities of Daily Living
   – Long Form (IADL-LF) for first administration
   – Short Form (IADL-SF) for subsequent administrations

☐ Hopkins Verbal Learning Task- Revised (NC06) – Immediate Recall trials only

☐ Stroop (NC07)

☐ Trail Making Test (NC01a)

☐ Symbol Digit Modalities Task (NC01a)

☐ HVLT-R (NC06) – Delayed Recall and Recognition trials (must start 20-25 minutes after completion of HVLT-R, Immediate Recall trials)

☐ Verbal Fluency (NC08)

☐ Letter Number Sequencing Task (NC09)

☐ Grooved Pegboard (NC10)

☐ WRAT-3 (NC02a) – English and Spanish speakers (only for those participants who missed initial administration as indicated on Visit Control Sheet)

☐ WAT (NC02b) – Spanish speakers only (only for those participants who missed initial administration as indicated on Visit Control Sheet)

☐ WTAR (NC04) – English speakers only (only for those participants who missed initial administration as indicated on Visit Control Sheet)

☐ Stress Assessment Questionnaire (PTSD)

AFTER PARTICIPANT’S VISIT:

☐ Review all forms and complete scoring as instructed. If you are uncertain about scoring any of the forms, discuss this with your site “gold standard” psychometrician. You can also fax your forms to the WIHS Central Cognitive Test Scoring Center (see below) for review.

☐ If participant does not complete ENTIRE NC Battery, then complete Form NC05 (Interviewer Feedback) to record why the Battery was not completed.

☐ The first 10 administrations of the NC Battery by each interviewer must be evaluated by the Central Cognitive Test Scoring Center. To do this, please fax all forms (except the IADL and the PTSD) and participant test pages for the first 10 administrations of the NC Battery by each interviewer to Jessica Oakley for review (email joakley@psych.uic.edu; fax # 312-413-4265). At the end of visit 30, please also send the remaining test forms for the HVLT-R and Verbal Fluency tests only, in bulk, either electronically as a PDF or via FEDEX to the following address:

   Jessica Oakley
   Women’s Mental Health Research Program, Room 316
   Neuropsychiatric Institute, South Tower
   912 S. Wood St. (M/C 913)
   Chicago, IL 60612
APPENDIX B: NEUROCOGNITIVE STUDY INTRODUCTION
WOMEN’S INTERAGENCY HIV STUDY
NEUROCOGNITIVE STUDY INTRODUCTION

BEFORE BEGINNING ADMINISTRATION OF THE NEUROCOGNITIVE BATTERY, GIVE THE FOLLOWING INTRODUCTION TO THE PARTICIPANT:

"Now we are going to do some tasks that involve solving problems and memory. These tasks have nothing to do with how smart you are. Even so, when some women take these tasks, they begin to feel like they are back in school or start to feel badly about their ability to answer the questions. We want you to know that no one gets all the answers correct on these tasks. The tasks are designed to have some very difficult questions that most people can’t answer. Remember that the most important thing is to try your best.

These tasks are very important because this is the first study like this among women. Up to now, this research has only been done in HIV-positive men. It is important for us to find out whether aging, life stress, and menopause interact with HIV to affect thinking and problem solving."

We want to provide you with an ideal testing environment that will allow you to perform to the best of your ability. We ask that you please help us to do this and minimize any distractions by turning off or silencing any cell phones and pagers if you haven’t already."

PROMPT: READ THIS SCRIPT IF ENGLISH IS NOT THE PARTICIPANT’S PRIMARY LANGUAGE:

"This study measures memory and other thinking abilities. For example, we will be asking you to remember a list of words, read and pronounce words, and to quickly come up with words that begin with a specific letter of the alphabet. Now I want to know whether you think you can do your best on these tests in English or Spanish. This is the language that you are most comfortable, fluent, and familiar speaking. It is usually your first language or the language you speak at home, but it does not have to be. Keep in mind that we will do all the tests in the language you choose, and we won’t be able to switch to another language when we see you again. So, would you say you are most familiar, or fluent in English or Spanish?"
AFTER FINISHING ADMINISTRATION OF THE NEUROCOGNITIVE BATTERY, GIVE THE FOLLOWING CLOSING STATEMENT TO THE PARTICIPANT:

“Thank you very much for your participation. I can’t give you specific feedback about how you did today because these tests are only for research purposes and this is not a clinical exam. If you are concerned about your memory or your performance on any of these tasks, then you should address these concerns with your primary care provider.”
APPENDIX D: WIHS NC BATTERY SCORING ISSUES LOG
**WIHS NC BATTERY SCORING ISSUES LOG**

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*Note: Please copy Erin Sundermann ([erin.sundermann@einstein.yu.edu](mailto:erin.sundermann@einstein.yu.edu)) and WDMAC ([jhsph.wdmac@jhu.edu](mailto:jhsph.wdmac@jhu.edu)) on emails regarding scoring issues in order to get confirmation on scoring decisions.*
APPENDIX E - NEUROCOGNITIVE (NC) WAVE 5 SCHEDULING GUIDELINES

1. **Gold Standard, Ideal Goal #1:** Do NC testing on every WIHS participant two years from the time of the last NC administration (i.e., do wave 5 NC two years from wave 4 NC completion) and do the NC battery on the same date as the WIHS core date.
   - Use the wave 5 NC date window and expected visit # as a guide.
   - Schedule the wave 5 NC on the WIHS core visit date that will fall within that date range. Don’t rely solely on the NC visit # as a guide.
   - Whenever possible, strive to complete the NC batteries on-time, every two years from date of last NC battery. This is the best practice, for quality assessment of NC changes over time amongst the cohort population and for quality data analysis.

**Goal #2 (if goal #1 cannot be achieved) is JUST DO IT!** Complete wave 5 NC testing, whenever it can be done within the wave (visits 46-49). Do everything possible to assure that each eligible WIHS participant completes a NC administration sometime in the Wave 5 time period (visits 46-49), even if you are unable to schedule the wave 5 NC in the wave 5 date window for the participant.
   - For instance, if a participant was due to have wave 5 NC on her visit 46 WIHS core date, but NC is not done on the core date, then schedule NC as soon as possible after her WIHS visit 46 core date. Then, if NC is still not done prior to the start of WIHS visit 47, try to do NC on the WIHS visit 47 core date (and at visit 48 if not done visit 47, and at visit 49 if not done visit 48). **Do NOT skip wave 5 NC just because it could not be done at the 2-year point!** Out-of-window NC completion (early or late) is better than no NC completion at all during the NC wave cycle, visits 46-49.

2. **Use the Wave 5 NC date window (not solely the WIHS visit #) as the guide to when to schedule wave 5 NC in conjunction with the V46-V49 WIHS core visit.** The wave 5 NC window is calculated to be 2 years from the wave 4 NC visit completion date (or 8 years from baseline NC completion date, if no wave 2, 3 or 4 was ever completed), but every 4th WIHS visit may or may not fall exactly at the 2-year point, if participant has not been seen at regular 6-month time intervals. Try to do the wave 5 NC battery on a WIHS core date that will fall within the wave 5 due-date window.

3. **IF PARTICIPANT DID NOT COMPLETE WAVE 4 NC DURING VISIT V42-V45 (BUT HAD A BASELINE NC):** Use your best judgment to schedule the wave 5 NC battery, based on knowledge of the participant’s WIHS visit attendance history. The fact that she failed to complete wave 4 NC during any of visits 42-45 probably indicates that she is not a regular WIHS attender for some reason. You need to capture her for wave 5 NC whenever you can. If she has become a regular WIHS attender during NC wave 5 and staff are confident that the wave 5 NC can be done at the 8-year point (from baseline NC), that’s ideal. **But don’t hesitate to do wave 5 NC anytime**
(early or late) if staff are concerned that the participant may not show up for a future WIHS core visit when the NC battery is due.

4. **IF PARTICIPANT HAS NEVER COMPLETED A WIHS NEUROCOG BATTERY**, do a baseline NC battery ASAP, if eligible.

- Eligibility for WIHS NC battery: Completes WIHS interview in English (even if bilingual).
- Exclusion criteria for WIHS NC battery: Completes WIHS interview in Spanish.
- **NOTE:** Blind women or women with only partial or no use of their arms/hands can still participate in WIHS NC testing but should be administered only the NC tasks which fit their physical ability.