NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON AGING
INTRAMURAL RESEARCH PROGRAM

Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS)

Wave 4 Protocol

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Contents

1.0.0 HANDLS Study Staff Roster 1
2.0.0 Statement of Compliance 5
3.0.0 List of Abbreviations 6
4.0.0 Protocol summary 7
5.0.0 Précis 8
6.0.0 Background and Scientific Rationale 9
7.0.0 Study Objectives 10
7.1.0 Sub-studies Objectives 17
7.1.1 Neuroimaging Sub-study (HANDLS Scan) 17
7.1.2 Circadian Rhythm Sub-study 19
7.1.3 Subjective Experience of Diabetes Sub-study 20
8.0.0 Expected Risks and Benefits 22
9.0.0 Eligibility 22
10.0.0 Subject Enrollment 23
11.0.0 Study Design and Procedures 23
12.0.0 Procedure Description 27
13.0.0 Collection and Storing of Human Sample Specimens and Data 33
14.0.0 Data Collection and Management Procedures 34
15.0.0 Quality Control 35
16.0.0 Statistical Considerations 35
17.0.0 Regulatory Requirements 36
17.1.0 Informed Consent 36
17.2.0 Compensation 37
17.3.0 Subject Confidentiality 38
18.0.0 Participant Safety, Adverse Events, & Problem Reporting 39
18.1.0 Participant Safety & Intent to Treat 39
18.1.1 Poorly controlled hypertension and related medical non-compliance 39
18.1.2 Poorly controlled diabetes mellitus and related medical non-compliance 40
18.1.3 Poorly controlled asthma/chronic obstructive pulmonary disease (COPD). 41
18.1.4 Alcohol Withdrawal 41
18.1.5 Seizure Disorder 41
18.2.0 Adverse Events & Unanticipated Problem Reporting 42
18.3.0 Reporting Waiver 42
19.0.0 Site and Clinical Safety Monitoring Plan 43
20.0.0 References 44

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Contractual Arrangements – **University of Delaware and Westat**

1. Type of Contract/ Agreement:	**2. Sources of funding:**
Agreement Type: [x]Contract [ ]Subcontract [ ]Technology Transfer Agreement [x] Data Use Agreement (DUA) [ ] Material Transfer Agreement (MTA) [ ] Cooperative Research and Development Agreement (CRADA) [ ] Memorandum of Understanding (MOU) [ ] Memorandum of Agreement (MOA) [ ] Letter of Agreement [ ] Confidential Disclosure Agreement [ ]If other; then specify: IRB Authorization Agreement Agreement Agreement Start Date: 2014 Agreement Expiration Date: upon completion of project Have funds been awarded? [x]Yes [ ]Pending [ ]No	[x]Institute/Department/Program Funds [ ] Another NIH Institute [ ] Another Federal Agency [ ] Foundation for the National Institutes of Health (FNIH) [ ]Industry [ ]Other Private Entity [ ]Other, specify: _____ **Name of Funder/s and/ or Sponsor/s:** _____ _____ _____ _____

2.0.0 Statement of Compliance

The HANDLS study will be conducted in accordance with the design and specific provisions of this IRB-approved protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the requirements set forth in the US code of Federal Regulation applicable to clinical studies (45 CFR 46, parts A through D) concerning informed consent and IRB regulations; and in compliance with the International Conference on Harmonization's guidelines for Good Clinical Practices (ICH GCP). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to the study participants. The Principal Investigator will promptly report to the IRB and the sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

3.0.0 List of Abbreviations

HANDLS..... Healthy Aging in Neighborhoods of Diversity across the Life Span
MRVs..... Medical Research Vehicles
SES ..... socioeconomic status
MRI ..... magnetic resonance imaging
DXA..... Dual-energy X-ray absorptiometry
DNA ..... deoxyribonucleic acid
AA ..... African American
DTI..... diffusion tensor imaging
ADC ..... apparent diffusion coefficient
LRC ..... Lighting Research Center at Rensselaer Polytechnic Institute
SOP ..... Standard Operating Procedures
SSB..... single strand breaks
DRC..... DNA repair capacity
SNP ..... single nucleotide polymorphism
GWAS..... genome wide association study
COGENT ..... Continental Origins and Genetic Epidemiology Network
CARe..... Candidate gene Association Resource consortium
NHANES..... The National Health and Nutrition Examination Survey
CKD ..... chronic kidney disease
ESRD..... end stage renal disease
KIM ..... 1 kidney injury molecule-1
FA ..... fractional anisotropy
GM ..... gray matter
WM ..... white matter
T2DM..... Type 2 Diabetes Mellitus
UMBC ..... University of Maryland Baltimore County
MINI ..... McGill Illness Narrative Interview
HIV..... human immunodeficiency virus
FTA..... fast technology for analysis
mRNA ..... messenger ribonucleic acid
AMPM..... Automated Multiple Pass Method
REALM ..... Rapid Estimate of Adult Literacy
TOFHLA ..... Test of Functional Health Literacy in Adults
WRAT..... Wide Range Achievement Test
IVA ..... Instant Vertebral Assessment
mrem ..... millirem
ATM ..... automated teller machine
FDA..... Food and Drug Administration
NIA..... National Institute on Aging
NIH ..... National Institutes of Health
OHRP..... Office of Human Research ProtectionProtocol Summary

4.0.0 Protocol summary

Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) – Wave 4

Short Title:	HANDLS
Conducted by:	National Institute on Aging, Intramural Research Program, Laboratory of Epidemiology and Population Sciences, Health Disparities Research Section
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Sample Size:	3720
Accrual Ceiling:	4000
Study Population:	The baseline HANDLS sample consists of 3720 community-dwelling African American and white adults aged 30-64. Participants were drawn from 13 neighborhoods (groups of contiguous census tracts) in Baltimore City, sampling representatively across a wide range of socioeconomic and income circumstances.
Accrual Period:	2004-2009
Study Design:	The heuristic study design is a factorial cross of four factors: age, sex, race, and SES with approximately equal numbers of subjects per "cell" (Figure 2 on page 23). HANDLS is planned as a 20-year longitudinal study of the 3720 individ-

	uals accrued (Figure 3 on page 23). Using our mobile medical research vehicles, we are revisiting each census tract for 2-3 months over the next 3 years.
Study Duration:	Start Date: 2004; End Date: 2024
Primary Objective:	The primary objective of HANDLS is to conduct a longitudinal study of minority health, aging, and health disparities focused on investigating the differential influences of race and socioeconomic status on health in an urban population.

5.0.0 Précis

The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study is an interdisciplinary, community-based, prospective longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among socioeconomically diverse African Americans and whites in Baltimore. This study investigates whether health disparities develop or persist due to differences in SES, differences in race, or their interaction. Planned as a 20-year longitudinal study, HANDLS is unique because it assesses physical parameters as well as evaluating genetic, biologic, demographic, and psychosocial parameters of African American and white participants over a wide range of socioeconomic statuses. HANDLS also employs novel research tools, mobile medical research vehicles, in hopes of improving participation rates and retention among non-traditional research participants. The domains of the HANDLS study include: nutrition, cognition, biologic biomarkers, body composition and bone quality, physical function and performance, psychology, genomics, neighborhood environment and cardiovascular disease. Utilizing data from these study domains will facilitate an understanding of selected underlying factors of persistent black-white health disparities in overall longevity, cardiovascular disease, and cognitive decline.

HANDLS recruited a fixed cohort as an area probability sample of Baltimore City from August 2004 through November 2009 as Wave 1 (Figure 1). HANDLS Wave 2 entitled *The Association of Personality and Socioeconomic status with Health Status – An Interim Follow-up Study* began in June 2006 under a separate protocol. It was designed as a follow-up telephone interview approximately 18 months after the initial examination (Wave 1) was complete. Wave 2 provided interim contact with study participants, and important interim information regarding their health. Now completed, wave 3 was the first follow-up examination and participants' second visit to our mobile Medical Research Vehicles (MRVs). The current protocol outlines Wave 4, the second follow-up examination and participants' third visit to our mobile Medical Research Vehicles (MRVs). Planned as a follow-up after 3-4 years, Wave 4 consists of health examinations, a telephone dietary-recall interview, renal function assessments, and optional studies of circadian rhythm, structural MRIs, and an evaluation of the subjective experience of diabetes mellitus.

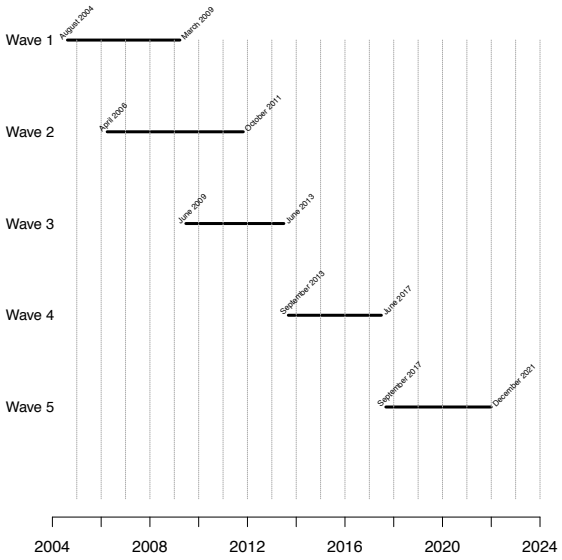

Figure 1. Present and projected HANDLS timeline

6.0.0 Background and Scientific Rationale

There are well-documented differences in health status among groups defined by age, race, ethnicity, and socioeconomic status (SES). Over the past decade or so, evidence from cross-sectional studies and nationally representative follow-ups suggests that there are persistent disparities among African Americans and other minority groups compared to Whites in morbidity[1-16] and mortality.[15,17-21] This is particularly evident in the steadily growing divide between well-educated white men and women and less educated African Americans.[22] Double jeopardy describes the constellation of health disparities conferred by old age and membership in a minority group.[23] Evidence suggests that there are unique disadvantages conferred by the combination of old age and minority status,[1-7,9,11-19,23-27] but the extent to which minority status is a direct cause of the disadvantage is unknown. Race, ethnicity, and SES are inextricably confounded in many studies. Membership in a minority group may be an indicator of the combinations of other effects such as low income, poor education, environmental exposure to toxic compounds, and lack of occupational opportunities.

Independent of the effects of race and ethnicity, SES accounts for differences in the functional status associated with chronic disease, but has only a small role in predicting prevalence of chronic disease.[16] Further complicating this relationship, physicians' assessments and treatment differ by race and sex.[24,28] Addressing these disparities in health status requires data about the differences in risks for chronic disease associated with race, ethnicity, and SES in all groups regardless of their majority or minority standing.

The scientific objectives of HANDLS are to establish a single-site prospective longitudinal epidemiologic study of health disparities in socioeconomically diverse African Americans and whites residing in the city of Baltimore. Specifically, we designed HANDLS to disentan-

gle the effects of race and SES on risk factors for morbidity and mortality, to examine the incidence and progression of pre-clinical disease, and to follow-up the development and persistence of health disparities, longitudinal health status, and health risks. The mechanisms or biologic and molecular pathways through which the health and longevity trajectories of individuals in American society are influenced are unknown at this time.

The present protocol focuses on predictors of change in cardiovascular function and fitness, risks for cerebrovascular conditions such as stroke, vascular dementia, and carotid stenosis, renal function, and pathological cognitive decline. We chose these specific areas as representing the health issues that are among the most prevalent, but least understood, in African Americans and low SES urban dwelling whites who have health burdens similar to African Americans. Specifically, we will measure heart function by echocardiogram, muscle strength by grip strength, chair stand and single leg stand exercises, body composition by dual photon x-ray absorptiometry (DXA), cognitive performance with cognitive and neuropsychological tests, and neuroimaging parameters by structural MRI.

We assess each of these areas by separate procedures for which we will investigate cross-sectional differences and longitudinal change within this sample and by comparison with other samples, particularly the National Health and Nutrition Examination Studies and other studies with which this study shares many procedures and tests. We will combine these measures in various ways to examine the risks for pathological outcomes such as stroke, dementia, and loss of functional independence.

7.0.0 Study Objectives

The primary objective of HANDLS is to conduct a longitudinal study of minority health and health disparities focused on investigating the differential influences of race and socioeconomic status on health in an urban population.

The scientific research questions for this interdisciplinary epidemiologic study of minority health and health disparities are:

(1) Do race and SES influence health disparities independently or do they interact with several factors (race, environmental or biologic factors, and cultural or lifestyle practices)?

(2) What is the influence of SES and race on age-related declines in function in an urban population?

(3) What is the influence of SES and race on the incidence and natural history of age-related disease?

(4) Are there early biomarkers of age-related health disparities that may enhance our ability to prevent or ameliorate the severity of these diseases?

For specific systems we will test the following hypotheses during Wave 4 of HANDLS:

Cardiovascular. (1) There will be significantly greater decline in cardiovascular health status as a function of SES and race independent of the effects of age in both men and women; for example, left ventricular mass, an important cardiac risk factor, is greater in African Americans than whites and is greater in African Americans of lower SES as compared to age-matched African Americans with higher SES, in both men and women; (2) Endothelial dysfunction is known to be more prevalent among African Americans. We hypothesize that it will not only be more prevalent in African Americans but also in low SES whites and those with evidence of oxidative stress markers because poverty and oxidative stress will be important modulating factors of endothelial function; (3) low SES will also correlate with lower Ankle-Brachial Index (ABI) values.

Body composition and bone quality. Compared to white adults of comparable age, African Americans have: (1) A higher proportion of fat to lean mass of the total body, trunk and extremities, and greater odds of meeting DXA-defined criteria for sarcopenia and sarcopenic obesity; (2) Faster loss of lean mass, greater accumulation of fat mass and greater increase in the proportion of fat to lean mass of the total body, trunk and extremities, and greater risk of transition to sarcopenia and sarcopenic obesity; (3) Faster and earlier decline in bone density; and, (4) These associations are correlated with, and perhaps mediated by, differences in health habits such as nutrition, physical activity, and alcohol consumption.

Cognition. The rates of decline of various cognitive abilities will be the same in all groups regardless of race, ethnicity, or SES.

Muscle Strength. (1) African Americans have the same trajectory of muscle loss as other ethnic or racial groups after accounting for differences in occupational history, nutrition, and body mass and composition; (2) All ethnic and racial groups will show the same relationships among changes in muscle strength, physical activity, and cardiovascular fitness regardless of socioeconomic factors, nutrition, and comorbid conditions such as diabetes; and, (3) The greater strength reductions at older ages among lower SES individuals will be attributable to their greater severity of chronic diseases

Covariates. Other variables such as nutrition, environment and neighborhood effects, genetic make-up, family history, activity level, access to health care, prevalent medical, dental, psychiatric conditions, caregiving status, renal function, oxidative stress, and DNA repair capacity may modulate the effects of SES and race on cardiovascular, musculoskeletal, and cognitive functioning. For example:

Nutritional intake assessed by two 24-hour dietary recalls will examine the effects of race socioeconomic status (SES) on nutritional status and identify nutritional factors that may contribute to health disparity in cardiovascular and cerebrovascular health and cognitive function.

Oxidative stress and inflammatory state. As a translational research study, HANDLS permits investigation of health disparities in terms of socioeconomic, socio-cultural, and psychosocial parameters. HANDLS allows us to define a medical/biologic phenotype that may be amenable to dissection by bench scientists examining the molecular aspects of

aging, disease and disability. The early appearance and increased severity of age-associated disease among African Americans and low SES individuals suggests that the factors contributing to the emergence of health disparities may also induce a phenotype of 'accelerated aging'. While others have attributed this to racism and other socio-cultural factors, we seek to understand the underlying biologic, genetic, and environmental factors that may result in this phenotype that ultimately contributes to the disparate life expectancies for low-SES and minority sub-populations. The health disparities induced phenotype of accelerated aging may be biologically similar to heritable 'progeroid' syndromes whose manifestations include increased susceptibility to oxidative stress, premature accumulation of oxidative DNA damage, defects in DNA repair and higher levels of biomarkers of oxidative stress and inflammation. While genetic background, environmental and behavioral factors influence health outcomes in all populations over the lifespan, health disparities may be the end product of an accelerated trajectory of dysfunctional interactions of these factors in populations at high risk or with high levels of risk exposure. Every day, cells are faced with damage to their DNA, the most common form of oxidative, which includes single strand breaks (SSB) and oxidative base damage. Normally, cells repair oxidative DNA damage through various repair mechanisms. Unrepaired DNA damage can cause mutations that can lead to age-related diseases, aging, and death. Oxidative DNA damage includes single strand breaks (SSBs) and oxidative base damage. An increased baseline level of oxidative DNA damage is associated with several age-related diseases including: cardiovascular disease [29], diabetes mellitus,[30] cancer,[31] neurodegenerative disease,[32] and end-stage renal disease.[33] The level of oxidative DNA damage depends on a variety of factors. They may include age,[31] environmental exposure to genotoxic factors,[34] smoking,[35] ethanol intake,[34] and intracellular and extracellular metabolism.[36]

HANDLS examines this hypothesis by measuring biomarkers of oxidative stress and inflammation, assessing levels of the most widely studied oxidative DNA adducts, and measuring DNA repair capacity (DRC) in study participants. In addition, other important biomarkers of oxidative stress are being evaluated. These include glutathione levels, fluorescent heme degradation products, and plasma carbonyl levels. Measures of inflammatory states include the pro-inflammatory cytokines , and C-reactive protein. Prospectively measuring biomarkers of oxidative stress in a longitudinal study may clarify whether oxidative stress plays a pivotal role in aging and in the development and or progression of age associated disease. It may also provide insights into the different trajectories of aging observed in individuals.

Genetics. Current technological advances in genotyping permit high throughput whole genome single nucleotide polymorphism (SNP) genotyping to proceed with the overall goal of examining the genetic contributions to the development of multi-gene complex clinical disorders. Of equal importance is the contribution this new knowledge will provide in furthering the examination of the genetics behind the differences in medicinal drug responses frequently seen in individuals as well as to the discovery of new drug targets for a range of diseases with persistently high morbidity and mortality. Our primary aim is to identify the genetic factors that are associated with age-associated health disparities. We hypothesize that the prevalence and severity of age-associated disease in minority populations is related to in some cases genetic susceptibility factors. Genotyping will focus on identifying specific

SNPs that may be related to disease susceptibility and or the severity of disease states and metabolic conditions that disproportionately affect this longitudinal cohort over the next 20 years. Examining the prevalence of these genetic polymorphisms is critical to understanding not only the association between the polymorphism and the disease but the molecular and biological functional outcome of these polymorphisms. Although race itself is not a definitive biologic factor but largely a proxy for social, cultural behavioral and environmental factors it is critically important for us to attempt to understand the role of genetic susceptibility to specific age-related heath disparities and clinical characteristics. The first step to gaining this understanding is to identify risk alleles for common diseases through genome wide association studies (GWAS). However, most of the early GWAS analyses failed to include diverse cohorts enriched for sub-populations at greatest risk. Therefore inclusion of diverse population groups will hopefully enhance understanding of the effects of various genetic variants in different groups who may have different environmental exposures.

Whole genome SNP genotyping using the Illumina Infinium II platform for the first 1000 participants has been completed. Planned work will proceed in conjunction with GWAS consortia including: the Continental Origins and Genetic Epidemiology Network (COGENT) and the Candidate–gene Association Resource consortium (CARe). Initial areas of research have focused on renal, metabolic, hematologic, and cardiovascular characteristics or conditions. Analysis of the data set is underway to determine genetic associations with hypertension, renal disease, cardiovascular disease, stroke and other age associated health disparities. In addition, other GWAS studies that have been completed focused on height, platelet count, water balance, and serum sodium concentration. Supplementary genotyping and sequencing will be performed dependent on the availability of funds.

Epigenetics. The disproportionate incidence and mortality from age-associated disease may also result from epigenetic mechanisms such a DNA methylation. One theory of aging focuses on the role of genes and the epigenome in the development of the aging phenotype. We will examine the hypothesis that human disease and disability may result from DNA modifications that are not the result of changes in the coding sequence of genes. The clinical relevance of DNA methylation states in the development of age-related disease has yet to be understood on a population basis. There is variation in methylation states from individual to individual. This may be related to age, gender, environmental exposure, and other genetic factors. Is it possible that our hypothesized phenotype of accelerated aging phenotype seen in low SES and minority communities is related to epigenetic factors such as methylation? We will examine methylation states within this longitudinal cohort to attempt to understand whether methylation states are associated with the premature development of age-associated disease. Because there is limited information about methylation status of lymphoid cells, we have chosen to employ DNA isolated from the buccal cells for this study. This is also likely the best source of DNA in our urban based cohort at higher risk for environmental exposures from air pollution and because of the prevalence of tobacco and alcohol use within this cohort at higher risk for the development of aerodigestive cancers of the lung and esophagus. Our investigations will focus on identifying DNA methylation patterns factors that are associated with the development of health disparities and with changes in human DNA repair capacity. These studies will examine the gene promoter methylation status in

buccal mucosa cell DNA from HANDLS participants. Assessing this at baseline and longitudinally may permit us to identify molecular markers of disease susceptibility especially for aerodigestive malignancies that are characterized by disproportionate incidence and mortality rates in African Americans.

Renal function. The National Health and Nutrition Examination Survey (NHANES) reports that while chronic kidney disease (CKD) prevalence among Americans older than 20 years of age was 16.8%, rates for non-Hispanic Blacks and Mexican Americans were higher (19.9% and 18.7% respectively. This disparity is significantly highlighted when assessing the prevalence of stage 1 CKD. Prevalence of CKD 1 among non-Hispanics whites is 4.2% compared with 10.2% for Mexican Americans and 9.4% among non-Hispanic Blacks. The statistics for End-Stage Renal Disease (ESRD) mirror these disparities; African Americans have a 3.6 fold higher rate than whites and Hispanics have a 1.5 times higher prevalence rates than the U.S. non-Hispanic white population.[37]

The risk factors for CKD are multifaceted and difficult to dissect; they include: hypertension, diabetes mellitus, smoking, race, age, obesity and heart disease[38]. However, it is clear that other etiologic factors may also play a role including behavior, genetics, and the physical and sociologic environment as has been shown for ESRD [39-41]. Because of the complexity of the factors that influence the development of chronic kidney disease and the significant impact CKD and ESRD have on quality of life, disability and life expectancy [39-43], we set out to examine predictive factors for CKD, including poverty, genetics, food security, diet, and race. In hopes of providing early identification of participants with CKD, to improve outcomes and awareness of CKD among participants, serum Cystatin C levels and urinary kidney injury molecule-1 (KIM-1) will be measured in each participant. Cystatin C has been selected because the literature suggests that it may provide a more accurate estimate of GFR, especially when GFR is only mildly depressed.[44] Additionally, Cystatin C has been found to be a better predictor of cardiovascular mortality than creatinine among persons with mild CKD. Urinary KIM-1 has recently been shown to be increased in patients with non-diabetic CKD and may be an important target for treating CKD.

Caregiving. Health disparities may result from various forms of stress including psychological stress. Many studies have linked caregiving with significant levels of chronic stress for caregivers. This chronic stress is moderated by socioeconomic status, the condition and disabilities of the individual for whom care is provided, social support, and the age of the caregiver. Although depression is a well studied health outcome among caregivers, other studies have shown that overall health, compliance with appropriate health related behaviors, and diet are all negatively influenced by caregiving. There are a few studies that have examined the effects of accumulated multiple social roles (i.e. caregiver, spouse/partner, parent, and employment, and volunteer) and role combination (e.g., elder care, only; child care only; elder care and child care.[45-50] This body of literature supports either the scarcity hypothesis, occupancy of more than one role is associated with poor well-being (e.g. Hong & Seltzer[46] while others support the enhancement hypothesis, occupancy of more than one role is associated with positive outcomes (e.g., Adelmann[51]). Most of this research sampled primarily white caregivers. There remains a lack of research focused on middle and older

aged, African-American women who are in multiple caregiving roles. To examine the influence of multiple caregiving roles (i.e., occupancy of more than one caregiving role) on the physical and mental health outcomes of HANDLS participants with specific focus on grandmother caregivers. This aim is to gain greater understanding about the relation between multiple caregiving roles (i.e., occupancy of more than one caregiving role), and health status (physical and mental) among HANDLS participants. This proposed study could extend the caregiving literature in several ways. First, it will assess the influence of multiple caregiving roles on health status of caregivers, across race/ethnicity, class and gender. Previous studies lacked sample diversity and primarily focused on low-income, African Americans, or grandmothers. Inclusion of a diverse sample will allow the researcher to examine intra and inter variations based on caregivers' age, race and ethnicity, sex and education. Second, it will assess the influence of role combination, (e.g. elder care, only; grandchild care only; elder care and grandchild care). Several researchers found that role combination may have a greater influence on health outcomes than simply the number of roles.[46]

Health literacy. Examination of the underlying factors of health disparities requires investigation of health literacy among populations at risk. Health literacy is defined as "the degree to which individuals can obtain, process, and understand the basic information and services they need to make appropriate health decisions…"[52] In 2004, the IOM estimated that almost 90 US adults million adults had low levels of health literacy.[53] Work by multiple groups has linked health disparities to low levels of literacy and these disparities are not solely linked to income level, race or education levels.[54-56] Older adults are also more likely to have low levels of health literacy as well as those with multiple chronic illnesses or co-morbid conditions.[57-60] Reading and numerical skills are required to function effectively in health care environment. Inadequate health literacy affects several factors that may influence health disparities as well as severity of age-related conditions such as preventive care, medical compliance, and health care expenditures. Health literacy may also influence the recruitment and retention of low SES and minority individuals in clinical research. One of the gaps in our knowledge about reducing health disparities is how to modulate associated factors like health literacy to promote the reduction of health disparities. As many suggest, it is essential to integrate health literacy assessments in disparities research.[61]

We will assess health literacy in Wave 3 of HANDLS to examine its and to investigate the influence of race, sex, age, income, education and reading level on health literacy. We will also assess the associations of health literacy with chronic medical conditions, multiple co-morbidities, cognition, and symptoms of depression and other psychological factors. It provides an adequate evaluation of an individual's ability to read and understand health materials. Perhaps most significantly, we will use the health literacy data to develop appropriate HANDLS research study materials as well as health education messages tailored to our study population. Although we now assess all participant study materials for culturally competent and proficient communication as well as for readability using the Flesh-Kincaid Readability formula, it is likely that this additional information about health literacy levels will better inform our material preparation and review process. Given the very high smoking rates in our population, it is clear the standard health education messaging has not been effective. We

hope that by evaluating health literacy in our population we can add to the literature information that will improve health education messages for vulnerable, at risk populations.

Assessment of activity by ActiGraph accelerometers. Interest has grown in the role of daily activity as an important behavior underlying many common risk factors for poor health including obesity, blood pressure, insulin metabolism, and other metabolic traits. Vigorous physical activity is associated with better health status and recent literature suggests that, even accounting for vigorous physical activity, physical inactivity may be an independent risk factor for poor health. Physical inactivity is an important health risk factor and strongly related to disability, morbidity, and increased risk of mortality. Because daily activity and socioeconomic status are closely intertwined as risk factors, we have decided to measure activity using accelerometers.

Estimates of daily activity should include physical activity in the form of exercise and daily general activity as well as time spent sitting without movement. In epidemiological studies, physical activity data are typically collected through self-report. The commonly used methods of survey and self-report frequently yield physical activity data that are inaccurate and limited. Self-reported physical activity suffers from significant reporting bias attributable to a combination of social desirability bias, and estimating frequency and duration of physical activity is cognitively challenging. Many studies have shown that report of exercise tends to overestimate participation in exercise or other strenuous activity and underestimate time spent sedentary. Self-reported data has only modest correlation with gold standard methods of activity measurement. Therefore, accurate estimates of physical activity are crucial for both clinical and public health applications

The development of accelerometry as an objective measure of daily activity has opened up new possibilities for studying all intensity levels of activity levels from completely sedentary to vigorous activity over extended periods of time. Accelerometers capture force exerted when the body is in motion; they often capture forces in multiple directions and can be worn anywhere on the body. The National Health and Examination Study (NHANES) has included data on objective activity twice: first with an accelerometer worn on the hip and currently, with a wrist worn accelerometer. This latter position makes it feasible for the accelerometer to be worn 24 hours a day and the recordings can be put through a series of computer programs that allow assessment of physical activity over the course of the day.

These monitors capture the intensity and fact of movement. They can be used to track performance of an individual over time or they can be used to compare groups of individuals who share some common characteristic. In HANDLS, for instance, we can obtain and track features such as whether there are systematic differences in when people start and end their activity of the day, how much walking an individual does, how much time an individual spends in an upright position, and how much time an individual spends sedentary. The measurements may help to explain the association of other risk factors such as blood pressure, to health outcomes as a function of race, socioeconomic status, sex, and age, suggesting important pathways for intervention.

We will use 2 wrist-worn accelerometers that are about the size of a small bracelet. Participants will be given 2 wrist-accelerometer and instructed in their use during their clinic examination. They will be asked to wear the accelerometer for up to two weeks and to return the accelerometer to the clinic via a mailer that will be provided free of charge or they can be picked up by HANDLS staff members. This protocol has been implemented in other studies and works well in terms of a high rate of participation. The goal is to obtain at least 4 days of wear from each participant. Data will be downloaded onto a computer at the site of return and then recharged for distribution to another participant.[62-64]

Mobile Health. HANDLS will test the feasibility of providing cellular phones or small internet ready devices to determine whether the device will help to improve compliance with HANDLS physician recommended healthcare follow-up stemming from their HANDLS medical examination. We will send electronic reminders to participants about physician's treatment recommendations explaining the risks for further complications should their healthcare needs go untreated. For difficult to track participants, we will test whether providing the device will assist in maintaining contact between study visits and whether providing appointment reminders improves retention rates among the most difficult to track HANDLS participants.

7.1.0 Sub-studies Objectives

7.1.1 Neuroimaging Sub-study (HANDLS Scan)

There are pronounced health disparities associated with race and socioeconomic status (SES) in various brain health endpoints including stroke, dementia, cognitive decline, and functional disability.[65,66] Particularly potent race disparities in stroke incidence are apparent at strikingly young ages, with a four-fold increased risk of stroke mortality among 45-59 year old African Americans (AA).[67] Efforts are needed at disentangling the respective influences of race and SES in brain health, particularly early and subtle markers of brain pathology that predict future stroke, dementia, or cognitive and functional decline. Measures of subclinical or covert cerebrovascular disease assessed by magnetic resonance imaging (MRI), including gray matter and white matter volumes and white matter microstructure, offer such proven associations.[68,69] Identifying multi-level mediators of the relations of race and SES to subtle brain pathology is also crucial. Biomedical, behavioral, psychological, social, and environmental factors have been implicated as potential mediators of the relations of race and SES to a multitude of physical health outcomes,[70,71] but little is known about these pathways for brain health endpoints.[71,72] Recent quantitative MRI data in older adults revealed larger brain volumes, but greater white matter hyper-intensities in African Americans than whites.[73] The most pronounced relations of vascular disease to brain atrophy and white matter hyper-intensities were found in African Americans. MRI indices of subtle brain pathology have been associated with lower levels of cognitive and physical function and cognitive decline,[74,75] and may mediate relations of race and SES to these endpoints.

This protocol is a sub-study linked to the ongoing HANDLS study. In a subset of 500 HANDLS participants, we will assess total and regional gray matter and white matter volumes and white matter microstructure in 500 stroke- and dementia-free HANDLS participants

(250 African American, 250 white; 50% women; ages 30-64 at baseline) over the full range of socioeconomic status using quantitative MRI data, including volumetrics and diffusion tensor imaging (DTI). Please see appendix – Protocol for HANDLS Neuroimaging Study for specific study procedures.

We will address the following aims and hypotheses:

Specific Aim 1. Examine race- and SES-related health disparities in MRI-assessed measures predictive of future stroke, dementia, or cognitive decline, and evaluate whether these relations differ by sex and age. The primary outcome measures will include total and regional gray matter and white matter volumes quantified by voxel-based morphometry, ischemic lesion volumes, and total and regional fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) estimated by DTI.

Hypothesis 1. There will be significant interactive relations of race and SES with respect to MRI indexes of gray matter and white matter volumes, ischemic lesion volumes, and white matter microstructure such that lower SES African Americans will display the most extensive brain pathology, particularly in prefrontal regions. Moderated mediation by age and sex (i.e., that age and sex may moderate the meditational paths by which race and SES relate to brain outcomes) will be explored.

Specific Aim 2. Examine multi-level mediators of the relations of race and SES to brain MRI outcomes; potential mediators (i.e., vulnerability or resilience factors) include biomedical (e.g., cardiovascular risk factors, subclinical vascular disease, cardiovascular comorbidities), behavioral (e.g., diet, smoking, alcohol, physical activity), psychological (e.g., depression, vigilance, anger, stress, spirituality), social (e.g., social support and networks, racial discrimination), and environmental (e.g., neighborhood deprivation, access to health care) factors.

Hypothesis 2. The multi-level mediators of MRI-based measures of GM and WM will differ as a function of race and SES. For example, select psychological factors such as racial discrimination may be prominent influences in high SES African Americans (as per pilot data), whereas behavioral, social, and environmental factors may be the most prominent influences in low SES African Americans. Moderated mediation by age and sex will be explored.

Specific Aim 3. To examine whether MRI indexes of gray matter and white matter are proximal mediators of the relations of race and SES to cognitive and physical function.

Hypothesis 3. Lesser white matter integrity and lesser white matter and gray matter volumes, and higher ischemic lesion volumes will be associated with lower levels of cognitive (particularly executive) function and physical function. These associations will be most pronounced among lower SES African Americans. Moderated mediation by age and sex will be explored.

7.1.2 Circadian Rhythm Sub-study

African Americans in Baltimore are statistically more likely to exhibit higher rates of mortality and morbidity than age-matched whites. Disruption of circadian rhythms has been linked to a wide range of maladies from diabetes to cancer. To our knowledge no formal study of circadian disruption in African American populations has been undertaken, particularly in a natural setting.[76,77] The HANDLS cohort is an ideal population to compare circadian disruption among sub-populations in Baltimore. If shown that this population is in fact disrupted, non-pharmacological interventions can be then developed to increase circadian entrainment, and possibly, reduce risks in this population.

Circadian rhythms are a fundamental part of life. All species on Earth exhibit 24-patterns at behavioral, physiological, and cellular levels. Circadian disruption associated with a lot of maladies.[78,79] Light is the primary zeitgeber (time-giver) for the circadian system. Disruption of a regular, 24-hour pattern of light and dark leads to circadian disruption. The Lighting Research Center at Rensselaer Polytechnic Institute (LRC) has developed personal light exposure devices (e.g., the Daysimeter12) for deployment in natural settings.[76,77] The LRC has also pioneered analytical methods for quantifying circadian disruption in humans and in other species, including nocturnal rodents, called phasor analysis.[80] Phasor analysis is based upon the functional relationship between two periodic cycles. The Daysimeter12 measures actual light-dark cycles together with activity- rest cycles, and based upon phasor analysis circadian disruption can be measured. From the Nurse's Health Study our collaborators were able to quantitatively compare circadian disruption in dayshift and in rotating-shift nurses, the latter population being at higher risk of breast cancer than the former. Disease and mortality are exhibited differentially in subpopulations within the city of Baltimore. A totally unexplored area is the quantification of circadian disruption through ecological measurements of patterns of light-dark and activity-rest in these subpopulations to determine whether there is an association between circadian disruption and disease and mortality. This is an entirely plausible line of research because (a) circadian rhythms are essential for life, (b) circadian disruption is associated with a wide spectrum of maladies, including increased risk for cancer, diabetes, obesity, cardiovascular disease, and seasonal depression and (c) the ecological approach proposed here has been successfully demonstrated in several populations including, nurses, submariners, teens, young adults, and those with dementia.

This protocol is an ancillary project linked to the ongoing HANDLS study. In a subset of 100 HANDLS participants we will collect rest/activity and dark/light data using the Daysimeter12. Please see appendix entitled Ancillary Study - Circadian Rhythm Protocol for specific study procedures.

Aim 1: Collect rest/activity and dark/light data using the Daysimeter12 from participants in the HANDLS cohort using the Daysimeter12. It is hypothesized that those sub-populations with greater incidence of mortality and morbidity will exhibit greater levels of circadian disruption as determined by phasor analysis, based on the measured rest/activity and dark/light profiles, compared to those with lower incidence.

7.1.3 Subjective Experience of Diabetes Sub-study

Diabetes is the seventh leading cause of death in the United States.[81] Type 2 diabetes (T2DM) accounts for 90-95% of diagnosed diabetes and is predicted to nearly double over the next 15 years.[82] Diabetes disproportionately affects older adults, people of color, and individuals within urban environments,[82,83] with both African-American and women's diabetes mortality rates in particular increasing over the past several decades.[81,84] African-Americans and women also experience more diabetes-related complications.[85] These secondary conditions such as cardiovascular disease, stroke, dementia, diabetic neuropathy, amputations, renal failure and blindness compound what has grown into a public health crisis. Diabetes-related health care costs consume approximately 20% of US total health care expenditures and are expected to nearly triple by 2034.[81,86] Notably, 91% of these costs are associated with persons aged ≥45.[83] Addressing diabetes prevention and treatment, then, is a leading US public health priority.[87]

As with the prevalence of diabetes, urban, race, and gender disparities are found in diabetes treatment and self-management. With respect to geographic differences, medication adherence and self-management can be particularly challenging in urban environments with variable health care, transportation, food, and exercise opportunities.[88-92] Overall, African-Americans with diabetes are less likely to meet national exercise recommendations than whites.[93] Similarly, women are less likely to engage in diabetes self-management than men,[94] with older adult diabetic women in particular being less likely to meet national exercise recommendations.[93] Women also report high levels of self-blame regarding their illness,[95,96] numerous barriers to self-care,[97] and high rates of stress in managing care-giving responsibilities in addition to their own diabetes self-care.[98]

To address race and gender disparities, many diabetes control efforts call for "cultural sensitivity" and for the creation of programs that recognize the cultural context of high-risk populations.[99-103] With very few exceptions,[104-108] however, previous studies have not explored how persons with diabetes define and conceptualize their illness and illness management. Extant ethnographic research generally is limited to understanding diabetes in terms of the health beliefs of specific ethnic groups such as Latino, Native American, and Bangladeshi,[105,109-117] and may presuppose a belief system based upon group affinity. Furthermore, while research grounded in theories regarding cumulative disadvantage,[118] social ecology,[119] and stress,[107,111,120] have sought to explain race and gender differences in chronic conditions like diabetes with respect to broader political and economic disparities, few studies have examined how subjective understandings of diabetes and treatment vary both across and within male and female African-American and white groups.[121,122]

Finally, there is growing acknowledgement that decades of education and behavior change interventions have had mixed success in creating sustained diabetes self-management,[123,124] and renewed attention to patient-centered approaches to diabetes management is needed.[125] It is our premise that real progress in controlling diabetes cannot be made until we take seriously the individual's personal ideas about diabetes, such as the nature, definition, progression, priority and treatment of diabetes. Providers in particular need a deeper understanding of patients' subjective diabetes worlds. Through attention to the subjectivity of

diabetes, providers can promote clinical encounters that not only diagnose and educate, but that help patients to negotiate the beliefs and contexts that play a role in self-management.

The study, using ethnographic interviewing, will examine subjective conceptualizations of diabetes and self-management among male and female, African-American and white older adults in an urban environment. The study will provide critical information on the ways in which subjective definitions, subjective experiences, shared and idiosyncratic illness models and varied social contexts underlie participants' construction of and self-management of their diabetes. We will address the gap in understanding of the subjective experience of diabetes and the operation of cultural processes among male and female African American and whites with diabetes.

The interviews will be recorded on audiotapes. The audiotapes will be transcribed and stored digitally. All tapes and transcripts will be securely stored at the University of Maryland Baltimore County for 5-7 years following the completion of the study and will then be destroyed.

This sub-study involves a unique partnership between the NIA IRP Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) study, and the University of Maryland Baltimore County (UMBC), Department of Sociology and Anthropology, Center for Aging Studies.

Objectives. The 36-month study investigates the subjective construction of diabetes among African-American and white older adults, age ≥50, with T2DM, living in Baltimore City (n=80). We will use the McGill Illness Narrative Interview (MINI), a semi-structured ethnographic interview guide that we have modified for this study.[126] We seek to identify how local social, cultural, and material contexts inform participants' conceptions of their diabetes, perceptions of its risk factors and comorbidities, and their approach to managing their illness.

This study will address four specific aims:

Specific Aim 1. Identify participants' subjective accounts of their diabetes, including perceptions of the etiology, risk factors, symptoms, secondary conditions, and short and long term outcomes of their diabetes;

Specific Aim 2. Elicit participants' diabetes management practices, including perceptions and use of biomedical and lay (popular or folk) health care resources and self-management activities;

Specific Aim 3. Explore participants' accounts of the social context within which their diabetes is embedded, including how participants manage their diabetes with respect to other responsibilities and constraints, such as family care taking, job constraints, transportation, finances, time commitments, or other illnesses; and

Specific Aim 4. Determine the race and gender variations in participants' subjective understanding of their diabetes, their diabetes management strategies, if any, and the social contexts surrounding their diabetes.

Together, addressing these specific aims will provide rich, detailed insight into the subjective definition and construction of diabetes and diabetes management among urban older adults, and the race and gender variation in these constructions. We believe these aims will offer providers a better understanding of the subjective arenas in patients' lives that must be taken into account when working conjointly with patients to develop self-management plans.

Please see appendix entitled *Subjective Experience of Diabetes Protocol* for specific study procedures.

8.0.0 Expected Risks and Benefits

There is very little risk to participants in this observational study. The exposure to low dose radiation from the analysis of bone density and body composition by the densitometer and the risks associated with having blood drawn are the minimal risks.

The potential benefits to the participants include access to a full medical evaluation including screening for pathology in which early detection is advantageous. If the study doctor discovers any condition or problem, the information is provided to the participant immediately and their primary care doctor, with their permission. If the participant does not have a physician, efforts will be made to refer them for care. Participants will be reimbursed for time and inconvenience.

The potential benefits to society relate to improvement of overall health in a vulnerable population that currently bears a disproportionate burden of disease and disability in this country. Healthy People 2010, the nation's disease prevention agenda, have defined two national goals to reduce preventable threats to the nation's health.[127] The first is to increase the quality and years of healthy life and the second is to eliminate health disparities. However, in order to achieve this second goal it is critical to develop research initiatives that provide new insights into the relationship between psychosocial factors and health status by (1) incorporating biological measures into large scale epidemiologic health and survey research projects and (2) the development and inclusion of a diverse panel of biomarkers or biologic measures that evaluate biologic pathways that may be involved in the causal relationship between SES and health.[128] This is what HANDLS attempts to accomplish. If successful, HANDLS will provide unique information that will hopefully uncover findings that will provide a basis for the development of appropriate prevention and intervention strategies to reduce health disparities.

9.0.0 Eligibility

In this study we are examining age related disorders in a target population of African Americans and whites in a representative sample of Baltimore City residents.

Inclusion criteria: (1) Verified HANDLS participants (age 30-64 at baseline recruitment); (2) able to give informed consent; and, (3) must have valid picture identification.

Exclusion criteria: (1) Pregnancy (for the examination visit and the HANDLS Scan sub-study) a urine pregnancy test is performed with women of child bearing potential during the medical screening prior to any testing or procedures. If positive, participant will not be eligible for the examination visit until they are no longer pregnant. Participants with a positive pregnancy test will be invited to return for the examination visit and/or the HANDLS Scan once pregnancy is resolved (pregnancy testing is repeated at each encounter, if indicated). The Diabetes sub-study protocol does not pose increased risk so pregnancy status is not required or obtained); and (2) Current cancer chemotherapy or radiation therapy.

10.0.0 Subject Enrollment

Plan to re-contact participants for Wave 4. The HANDLS study has recruited a representative sample of 3720 whites and African Americans between 30 and 64 years old from 13 neighborhoods in Baltimore city in both low and high socioeconomic strata as a fixed cohort following the overall design. We have used several methods to remain in contact with our participants since they initially enrolled in HANDLS. Specific examples include sending regular mailings such as newsletters, holiday and birthday cards to the addresses we have on file, participation in the wave 2 interim study, mailing study updates and reminders with change of address cards, and periodic reviews of the Baltimore city judicial system public records and the National Death Index database. While this does allow us to remain in contact with many of our participants, there still exists a subset of participants for whom traditional methods will not be successful.

For Wave 4 we employ a tracing and tracking specialist whose primary responsibility is to focus on conducting investigative fieldwork and extensive tracing & tracking procedures to locate missing participants. This requires (a) physically driving through all identified HANDLS study neighborhoods in Baltimore City to previously known addresses for missing participants, communicating with current residents (and or neighbors) of identified households to assist in locating participants; (b) contacting participant's family or friends identified by the participant as persons to be reached if participant cannot be located (c) using search engines on the internet, Baltimore City judicial system public records, National Death Index, Division of Vital Records, and similar methods to locate current residence or to verify status of missing participants; and, (d) other tracing and tracking methods developed over time and with experience.

Including this strategy will allow us to make every possible effort to locate as many of our participants as possible. It is particularly crucial to have as little missing data as possible.

11.0.0 Study Design and Procedures

The HANDLS study is an interdisciplinary, prospective epidemiologic longitudinal study examining the influences and interaction of race and SES on the development of cardiovascular and cerebrovascular health disparities among minority and lower SES subgroups.

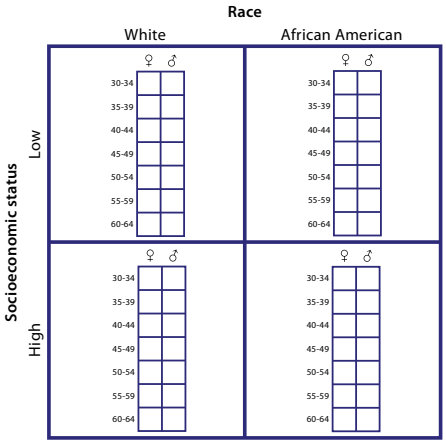

Figure 2. HANDLS sampling design

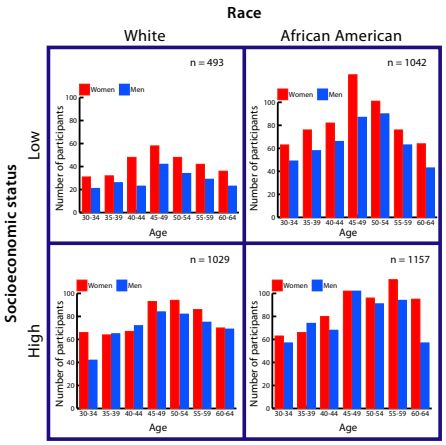

Figure 3. HANDLS baseline accrual

The baseline HANDLS sample consists of 3720 community-dwelling African American and white adults aged 30-64. Participants were drawn from 13 neighborhoods (groups of contiguous census tracts) in Baltimore City, sampling representatively across a wide range of socioeconomic and income circumstances. The heuristic study design is a factorial cross of four factors: age, sex, race, and SES with approximately equal numbers of subjects per "cell" (Figure 2). HANDLS is planned as a 20-year longitudinal study of the 3720 individuals accrued (Figure 3). Using our mobile medical research vehicles, we are revisiting each census tract for 2-3 months over the next 3 years.

The 13 neighborhoods identified were selected because they were likely to yield representative distributions of individuals between 30 and 64 years old who are African Americans and whites, men and women, and lower and higher SES.

Study sample. The study recruited an area probability sample of whites and African Americans between 30 and 64 years old from 13 neighborhoods in Baltimore City in both low and high socioeconomic strata as a fixed cohort following the overall design. By collecting a baseline assessment and 5 follow-up triennial assessments over approximately 20 years, there will be sufficient power (>.80) with 30 participants per group (race by SES by sex by age group) remaining after 20 years. There will also be sufficient power (>.80) to compare rates of change among groups after the baseline assessment.

Procedures. The study data for wave 4 is collected in three phases. We collect the first phase of the participant examination data on the medical research vehicles. These data include an interim medical history and physical examination since the baseline examination; dietary recall; cognitive evaluation; cardiovascular function: electrocardiogram, intimal medial thickness assessment by carotid Doppler, arterial stiffness measurement by pulse wave velocity, non-invasive baseline endothelial function assessment by peripheral arterial tonometry technology (Endo PAT II); assessments of muscle strength, lean body mass and bone density; laboratory measurements (blood and urine chemistries, hematology, biomaterials for genetic studies);measurement of activity via accelerometers (ActiGraph); and, an audio-administered questionnaire. For those participants who have difficulty ambulating independently, we recommend they complete the HANDLS home visit for wave 4 – phase 1

Phase 1A: Home Visit

Measure or Procedure	Estimated Duration
Consent (completed by phone or in-person)	20 minutes
Specimen Collection, Vitals and EKG	45 minutes
Cognition	60 minutes
Interim Medical History	30 minutes
Interim Physical Exam	45 minutes
Hand Grip	10 minutes
Questionnaires	15 minutes

Phase 1: Medical Research Vehicle Examination

Measure or Procedure	Estimated Duration	Location
Consent	20 minutes	MRV 2/3
Specimen collection (urine, blood, DNA)	20 minutes	MRV 3
Anthropometrics (height & weight)	5 minutes	MRV 1
Interim medical history	20 minutes	MRV 1
Interim Physical Exam	20 minutes	MRV 1
Dietary recall I	30 minutes	MRV 2
Cognition	40 minutes	MRV 2
Physical performance	15 minutes	MRV 1
Cardiovascular function measures	50 minutes	MRV 1
Questionnaires	50 minutes	MRV 2
Accelerometry	10 minutes	MRV 1
Body composition & bone densitometry (DXA)	5 minutes	MRV 1

Phase 2 – Post-examination Telephone Survey

Measure or Procedure	Estimated Duration	Location
Dietary Recall II & Supplement Questionnaire	30 minutes	Telephone

Phase 3 – HANDLS Wave 4 Sub-studies

Measure or Procedure	Estimated Duration	Location
Circadian Rhythm Study	30 minutes	MRV
Neuroimaging Study	90 minutes	UMB
Subjective Experience of Diabetes Study	90 minutes	Field

(see phase 1A table). Westat staff will collect the home visit data. Westat relies on the IRB of record for the National Institute on Aging to provide IRB oversight through an IRB reliance agreement. The roles and responsibilities of Westat are limited exclusively to activities related to data collection for the HANDLS Home Visit Program (HHVP), under the direction of Catherine Torres, Principal Investigator. Participants who did not have a wave 3 visit will be invited to complete an evaluation of health literacy and an echocardiogram.

We collect the second phase of HANDLS wave 4 as a telephone survey. It includes a repeated dietary recall interview and use of dietary supplement questionnaire. This data is collected and processed by Dr. Marie Kuczmarski and her colleagues at the University of Delaware. The University of Delaware relies on the IRB of record for the National Institute on Aging to provide IRB oversight (through an IRB Reliance Agreement), based on the stated roles and responsibilities of the University of Delaware.

A selected subset of participants is invited to participate in one or more of the optional studies that comprise the third phase of wave 4, the circadian rhythm ancillary study, the neuroimaging sub-study, or the diabetes sub-study. We conduct the circadian rhythm study on the MRVs. We conduct the neuroimaging study at University of Maryland School of Medicine and the Subjective Experience of Diabetes study is conducted in the field, at the participants' home or at a place of the participants' choosing.

Results. Participants receive a copy of their clinical laboratory findings within 2 weeks of their examination visit (home visit or MRV). If a result is critical or needs further evaluation, the HANDLS clinician will contact the participant by telephone as soon as possible following the notification (within 24-48 hours), and will send a copy of the result to the participant the same day. If the participant agrees and provides consent to release information, a copy of the results are also sent to the participant's physician. If the participant does not have a physician the HANDLS nurse or social worker will facilitate a referral for follow-up care. The HANDLS clinician is available for further consultation with the participant and or their physician to provide additional information and or to facilitate follow-up care.

Approximately 8-12 weeks following their visit participants receive a Participant Report Packet with a copy of the results from their blood and urine tests, EKG, and DXA Scan. If the participant agrees and provides consent to release information, a copy of the results are sent to the participant's physician.

HANDLS Scan reports of incidental findings are received from the University of Maryland within one week of the scan. If a result is critical or needs further evaluation, the HANDLS clinician will contact the participant by telephone as soon as possible following the notification (within 24-48 hours), and will send a copy of the result to the participant via certified US mail the same day. If the participant agrees and provides consent to release information, a copy of the results are also sent to the participant's physician. If the participant does not have a physician the HANDLS nurse or social worker will facilitate a referral for follow-up care. The HANDLS clinician is available for further consultation with the participant and or the physician to provide additional information and or to facilitate follow-up care.

12.0.0 Procedure Description

Collection and Analysis of Biomaterials

Blood and Urine Fasting blood samples for clinical tests, banking plasma, serum, and DNA. As a part of the medical evaluation, blood tests are performed to look for anemia and other blood disorders, diabetes mellitus, thyroid disease, hepatitis, prostate disease, HIV disease and kidney disease. We are also using some blood samples to study genes that may play a role in age-related diseases like Alzheimer's disease, heart failure, high blood pressure, and cancer. The total amount of blood drawn from each participant is about 87.5 milliliters (~6 tablespoons). A random urine sample is collected for urinalysis, measurement of microalbuminuria, and storage.

Risks. There are some risks from having blood drawn. There is a risk of an infection from the needle puncture. There is also a risk of a black and blue mark, and the participant may feel faint. It is common to have a small black and blue mark, but it disappears after a day or so. Some people may begin to perspire or feel nauseated. These risks are very small. Our medical staff is well trained and has drawn blood many times. There is no risk for urine collection.

Buccal cell collection. As part of the medical evaluation buccal mucosa cells are collected from saliva samples using the Genotek Oragene DNA self-collection kit from each consenting participant. Participants are asked to spit into a DNA collection system (a small sample cup) to collect buccal mucosal cells. The extracted DNA will be used for epigenetic analysis as well as human mRNA expression profiling.

Risks. This is a completely non-invasive self-collection system. There are no known physical risks.

Alternative buccal cell collection method. The Whatman FTA collection system will be used as a back-up buccal cell collection method. This system collects buccal cells using a foam tipped applicator which is placed into the mouth and rubbed on the inside of both cheeks for 30 seconds by the participant. The sample obtained is then transferred to the Indicating FTA cards. The extracted DNA will be used for epigenetic analysis.

Risks. Buccal mucosa smear risks include irritation of the inside of the cheek and/or gum line by the foam tipped swab used to collect cells and saliva.

Anthropometrics. We measure the height and weight of each participant.

Risks. None.

Medical history and physical examination. A physician or nurse practitioner performs an interim physical examination and medical history. The purpose of the physical examination and medical history is to document as unambiguously as possible any diagnosable conditions, to record medications and their frequencies and dosages, and to assess disabilities that might limit independent functional activities, that have developed or occurred since

their last examination on the MRVs. In addition, we will examine subjects to insure that they do not meet exclusionary criteria for any subsequent tests such as the DXA.

Risks. None.

Dietary Recall

Dietary recall interview. This measure is administered in both the first and second phases of data collection. We will ask participants to recall all of the foods and beverages they consumed during the previous 24 hours. An interviewer records the dietary recall using methods developed by the USDA called the Automated Multiple Pass Method (AMPM) that is supplemented by measurement aids and illustrations to assist in estimating accurate quantities consumed.

Nutrition supplement questionnaire. We ask participants to report all of the types and quantities of nutritional supplements they took during the previous 24 hours following the dietary recall. An interviewer also records usual supplement practices.

Risks. None.

Cognitive testing. We administer a battery of cognitive tests assessing memory, executive function, verbal fluency and knowledge, and spatial ability. The battery includes abstract matching, analog risk task, digital symbol substitution task, line orientation task, motor praxis task, N-back test, vigilance test, and visual object learning task. In addition to dementia screening using the Mini-Mental State Examination[129], we also administer the Wide Rage Achievement Test, and three executive function tests, Trail Making, the Stroop Test, and a judgment task based on the Mastermind® game. We assess symptoms of depression using the Center for Epidemiologic Studies Depression inventory (CES-D).[130] These tests are given in a private, quiet room with an experienced psychometric technician.

Risks. None.

Physical Performance Measures

The purpose of this performance battery is to estimate hand grip strength which has been associated with mortality and lower-extremity function and in this wave to carefully assess loss of functional capacity among participants. Use of these selected elements of the Short Physical Performance Battery and the hand grip will permit comparison to other nationally representative cohorts.[131]

Hand Grip Strength test. Handgrip strength in both hands, measured using an adjustable, hand-held, hydraulic grip strength dynamometer, is used as an overall assessment of physical strength and skeletal muscle function. Repeated measurement of grip strength over the follow-up visits will permit an estimate of strength loss over time. Grip strength is a commonly used indicator of health status and physical frailty and mid-life grip strength has been shown to be a strong predictor of early mortality.

The examination is done with the participant in the sitting position with the arm to be tested resting on the table and the elbow held at approximately a right angle. The dynamometer is held in the hand to be tested and is resting on a mouse pad. The participant is instructed to grip the two bars of the dynamometer in their hand, and to slowly squeeze the bars as hard as they can. The test is repeated on the other hand. This test is performed 3 times on each hand.

Exclusions. Participants who have had fusion, arthroplasty, tendon repair, synovectomy, or other related surgery of the upper extremity in the past 3 months will not be tested on the affected hand.

Sit-to-stand test. A commonly used performance-based test of physical function, the sit-to-stand test (also termed repeated chair stands), is used to assess functional status at study inception and to track loss of functional capacity over time. Using a standard armless chair placed securely against a wall, the participant is first instructed to rise from the chair without using arms and return to a seated position. If this is done successfully, the participant is then asked to repeat that movement 10 times. Performance, both whether 10 stands are completed and time to perform 5 or 10 stands has been strongly associated with onset of functional limitation, physical disability, institutionalization, and mortality.

Exclusions. There are no formal exclusions from attempting the single chair stand; inability to rise from a chair without using arms excludes participants from doing repeated chair stands.

Tests of Standing Balance

Side-by-side stand

The side-by-side stand test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support if a loss of balance does occur. This test requires the participant to stand with feet side by side for 10 seconds.

Semi-Tandem Stand

The Semi-Tandem stand test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support if a loss of balance does occur. This test requires the participant to stand with the side of the heel of one foot touching the big toe of the other foot for about 30 seconds.

Tandem Stand

The Tandem stand test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support if a loss of balance does occur. This test required the participant to stand with the heel of one foot in front of and touching the toes of the other foot for 30 seconds.

Single leg stand . The single leg stand test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support if a loss of balance does occur. This test requires the participant to stand on one leg with the other leg flexed at the knee and held about two inches from the floor. The participant is asked to hold the position for as long as they can, up to 30 seconds. The single leg stand has been found to be a sensitive test of standing balance for middle age and older adults and has been used in numerous epidemiologic studies of well elderly without mishap.[131,132]

Risks. There are very minimal risks associated with the Physical Performance Measures. The only risks are that there is a slight risk of falling and the participant may feel tired after these tests.

Cardiovascular Function

Resting electrocardiogram (EKG). We place electrodes on the participant's skin to record their heartbeats. By looking at the electrical pulse of their heart we examine the heart rate and rhythm, and check if they have had a heart attack.

Risks. None.

Carotid Arterial Blood Flow and Arterial Stiffness. Carotid Doppler ultrasonography is the method of choice for noninvasive, in vivo examination of the structure and function of the carotid arteries. Intimal-medial thickness has emerged as a potent predictor of stroke,[133-135] myocardial infarction,[135] coronary artery disease[136] and cardiovascular disease[134] independent of other traditional cardiovascular risk factors. In this study, we will perform high resolution B-mode ultrasonography on the left carotid artery, for the evaluation of systolic and diastolic common carotid arterial diameters, carotid arterial flow, intimal-medial thickness, and plaques. We will also evaluate the right carotid artery for the presence of plaques.

Risks. None are known

Pulse Wave Velocity (PWV). In addition to arterial wall thickness (IMT), central arterial stiffness is also increasingly recognized as an important predictor of cardiovascular morbidity and mortality.[137-143] Furthermore, recent studies suggest that vascular stiffness may precede the development of Hypertension. [144] Thus, vascular stiffness is emerging as a potent subclinical marker of cardiovascular disease. We propose to non-invasively assess arterial stiffness by measuring central arterial pulse wave velocity. This validated technique involves positioning of Doppler flow probes over the carotid, brachial and femoral pulses, simultaneously recording the waveforms, and gating them to the EKG. The distance between the recording sites is measured externally with a tape measure. Pulse wave velocity between 2 arterial segments is calculated by dividing the distance between the 2 sites by the time delay for the flow waves between these 2 sampling sites.

Risks. None are known.

Peripheral Arterial Tonometry via Endo PAT II System, The evidence suggests that the disproportionate cardiovascular disease risk among African Americans is not completely attributable to racial differences or to the standard cardiovascular disease risk parameters. Several sources of evidence suggest that the observed differences may be related to differences in the pathophysiology of the endothelium. The endothelium plays a central role in maintaining vascular tone and vascular homeostasis. Vasodilators including nitric oxide and prostacyclin and vasoconstrictors including endothelin-1, thromboxane A_2, and platelet activating factor are secreted by endothelial cells. Endothelial dysfunction results from decreased nitric oxide bioactivity. It is associated with vascular inflammation, vasoconstriction, and thrombosis and is one of the earliest manifestations of coronary atherosclerotic heart disease.[145] Numerous studies have demonstrated the increased prevalence of endothelial dysfunction among African Americans and is believed to play a critical role in the disparate incidence of hypertension and cardiovascular disease among this population.[146] What is the pathophysiological basis for the observed differences in arterial endothelial function? Endothelial function is modulated by race and sex. It is not completely understood how inflammatory factors, oxidative stress, and perhaps even the social determinates of health may modulate endothelial function.

We will measure endothelial function via Peripheral Arterial Tonometry (PAT) a non-invasive methodology to assess endothelium-mediated changes in peripheral vascular reactivity or vascular tone. The EndoPAT system measures nitric oxide mediated changes in vascular tone through the use of bio-sensors placed on the fingertips before, during, and after the occlusion of the blood flow in one arm by a sphygmomanometer. The release of the blood when the cuff is released leads to rapid return of blood flow which in turn causes a vascular dilatation (flow mediated dilatation and reactive hyperemia. The Endo-PAT II system provides an EndoScore or Reactive Hyperemia Index (RHI) which is a measure of endothelial function.

Risks. Occlusion of brachial artery may cause tingling in the arm and hand which will subside after the test. Patients s/p mastectomy should not have the cuff inflation performed on the side of the surgery. [147] [148] [145] [149]

Peripheral vascular assessment by ankle brachial index. The resting Ankle-Brachial Index (ABI) is calculated as the ratio of the systolic pressure in the ankle measured via hand held Doppler and sphygmomanometer at either the dorsalis pedis or posterior tibial artery and the systolic pressure measured at the brachial artery. The ABI is an indicator of peripheral artery disease as well as a prognostic marker of atherosclerosis and risk factor for future cardiovascular and cerebrovascular events.[150] [151] In this population at high risk for cardiovascular disease, measuring ABI will provide a benefit to participants at risk as well as an opportunity to evaluate covariates of abnormal ABI values in African American and low SES urban white cohorts. Participants will rest for 10 minutes, systolic pressure will be measured in both ankles and both with hand-held Doppler and properly sized sphygmomanometer.

Exclusions and Risks. Patients with open sores and ulcers at the ankle or antecubital fossa will be excluded as will those with AV shunts or grafts. Patients status post mastectomy or lower limb amputation will also be excluded.

Echocardiogram. Echocardiography is an ultrasound test that is the preferred exam for the non-invasive assessment of the structure and function of the heart. We measure the dimensions of the chambers of the heart, the thickness of the walls, and the systolic and diastolic function of the chambers. We also examine the structure and function of the valves. This test does not involve radiation and there are no exclusions. As time permits, this test is performed on only those participants who were not assessed in Wave 3.

Risks. Rare irritation from electrode placements.

Audio-administered questionnaires. We assess risk of poor mental health and questions about food security and income with an audio-administered (using a computer and headphones) questionnaire. Assistance is provided to the participants, if for example they have trouble seeing or reading the questions or are uncomfortable with using a computer.

Risks. None.

Health literacy. To assess health literacy in our population we employ two measures, the Rapid Estimate of Adult Literacy in medicine (REALM) and the Test of Functional Health Literacy in Adults (TOFHLA). The REALM assesses reading level through scoring pronunciation of 66 health care related terms by participants. It correlates with other measures of reading literacy and health literacy. The TOFHLA measures reading comprehension and numeracy and correlates well with the REALM and the WRAT. It provides an adequate evaluation of an individual's ability to read and understand health materials. As time permits, this test is performed on only those participants who were not assessed in Wave 3.

Risks. None.

Assessment of Activity via ActiGraph Accelerometry. Accelerometry as an objective measure of physical activity that permits assessment and study of all intensity levels of physical activity levels from completely sedentary to vigorous activity over a number of days. The accelerometer measures the existence and intensity of motion in terms of "counts." Data can be collected in short epochs (e.g., 1, 15, 30, or 60 seconds). The devices are small, easy to use, and can store data for multiple days. The accelerometer counts can be used to classify motion as sedentary, low intensity, moderate intensity, and high intensity based on cutoff points derived from validation studies. The BLUE band ActiGraph monitor will be worn on the RIGHT wrist. The BLACK band ActiGraph monitor will be worn on the LEFT wrist. The WRIST device should be worn all day and all night, including during sleep, but not during bathing, showering, or swimming**.** There are no exclusions for this test.

Risks. Skin irritation from the wristband may result; otherwise there are no other risks.

Bone density and body composition. We perform dual energy X-ray absorptiometry (DXA) on total body, lumbar spine, the hip and the Instant Vertebral Assessment (IVA) using a Discovery QDR series (Hologic, Bedford MA). DEXA delivers a small amount of radiation through an X-ray source while you lay on the scanner bed. Site-specific scans of the lumbar spine and right hip provide information on bone area (cm^2), and bone mineral density (g/

cm^2). Total body scan measures both body composition and bone mineral density, including bone mineral content (g), bone area (cm^2), bone mineral density (g/cm^2), total body tissue (g), fat mass (g), lean mass (g), lean mass plus bone mineral content (g), and percent total fat (%). The IVA provides an assessment of vertebral fractures. Results of the total body scan are presented for the body as a whole as well as for the arms, legs, trunk, head, pelvis, and spine.

Exclusions. DXA studies are not administered to pregnant women or individuals weighing greater than 450 pounds due to the densitometer's limitations.

Risks. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving minimal risk and necessary to obtain the research information desired. Although each organ receives a different dose, the amount of radiation exposure participants receive from these procedures is equal to a uniform whole-body exposure of less than 1 millirem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guideline established by the NIH Radiation Safety Committee for research subjects. The guideline is an effective dose of 5 rem (or 5,000 mrem) received per year (Table 2).

The NIH Radiation Safety Branch monitors equipment and technique used in this study.

Table 2. Radiation associated with DXA studies on spine, femur, vertebrae and whole body.

Scans	Millirems
Anterior-posterior spine, DXA	0.7
Anterior-posterior femur, DXA	0.7
Lateral Scan for IVA	7.0
Total body scan, DXA	1.0

13.0.0 Collection and Storing of Human Sample Specimens and Data

Intended use of the samples, specimens, and data. Samples and data collected under this protocol may be used to study the differential influences of race and socioeconomic status on health in an urban population. Genetic testing will be performed.

Labeling of stored samples. Participants' stored samples will be labeled with HANDLS identification numbers that only the study team can link to participants. Any identifying information about participants will be kept confidential to the extent permitted by law.

How samples, specimens, and data will be tracked? Samples are tracked using the NIA Biological Sample Inventory system following NIH guidelines.

Storage and release of samples. Samples of the participant's blood are kept in a research laboratory at the National Institutes of Aging, NIH or one of our contract facilities. The subject's samples are tested immediately, or they may be frozen and used later. Informed consent allows subjects to determine future use and use for genomic projects. The subject's samples are stored with a confidential code. Samples may be kept until no cells remain or until the investigators decide to destroy them. If the participant gives us permission some samples are released to other doctors and scientists who are not associated with this institute. The Clinical Director and the Principal Investigators on this protocol will decide which researchers may receive samples. The subject's samples may be used in their research only if the research has been approved by an Institutional Review Board (IRB) and is related to the original research questions association with this protocol or for other research purposes as indicated below. Access to the samples will be limited by storing samples in a locked room.

What will happen to the samples, specimens, and data at the completion of the protocol? The stored material will be used only for research and will not be sold. At the completion of the protocol, samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.

What circumstances would prompt the PI to report to the IRB loss or destruction of samples, specimens, or data? We will report any loss of samples (e.g., freezer malfunction to the IRB according to NIA protocol violation policy. In addition we will report to the IRB any loss of unanticipated destruction of samples or data.

Participants may decide at any point not to have to have their samples stored. In this case, the Principal Investigator will destroy all known remaining samples and report what was done to the participant and the IRB. This decision may not affect participants' status in this protocol or any other protocols at NIH.

14.0.0 Data Collection and Management Procedures

HANDLS data are collected electronically or manually on the MRVs, over the telephone and in participant's homes. Data are kept in medical charts in locked file cabinets. Electronic data is kept on password-protected computers. All clinical research forms are filed in locked file cabinets. These materials are kept within a locked medical record room. Access to all study data is limited to HANDLS staff and investigators. Data are coded and entered by ID number only. Collaborators receive ID numbers only. No other identifying information is provided with the data unless there is a data use or materials transfer agreement in place, consent has been obtained from the HANDLS participant and the collaborators have obtained required IRB approval.

Data analysis. The study employs a standard statistic software package depending on the independent and dependent variables being analyzed. Data analyses include logistic regression and mixed effects modeling.

Data sharing agreement. Data generated by the HANDLS study is available through several mechanisms including publications, presentation of results at national scientific meetings,

and via a proposal review mechanism routed through the HANDLS principal and co-investigators working group.

The HANDLS web site (http://handls.nih.gov) contains a data dictionary for each of the study domains outlining available data sets. This website also describes the proposal submission process for investigators who would like to use HANDLS data or biomaterials. Proposers are required to submit an electronic HANDLS concept sheet detailing the hypotheses and specific aims of the proposals as well as the required data sets and/or biomaterials. These proposals are reviewed by the HANDLS Working Group. Meritorious proposals are assigned a HANDLS Investigator to serve as liaison and collaborator working with the successful proposer facilitating the completion of the NIA and NIH data transfer or material transfer agreements required by federal regulations and to access and use the data set (s) or biomaterials required for the approved proposal. Proposals not completed and submitted for publication within the time frame stipulated in the proposal will be re-negotiated or terminated.

Data safety and monitoring. No data or safety monitoring board is required. The Principal Investigator will monitor and evaluate the progress of the study, including periodic assessment of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of contractors and other factors that can affect study outcome. This monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

15.0.0 Quality Control

All data for the HANDLS study is collected by following detailed Standard Operating Procedures (SOPs) as outlined in the HANDLS Operations Manual. The majority of data is collected electronically, in real time, and is monitored at regular intervals for accuracy and adherence to the protocol by HANDLS computer programmers and information technology specialists. Manually collected data are stored in the research medical record and are reviewed for accuracy and completion daily by the HANDLS Medical Records Specialist. The HANDLS Nurse Practitioner selects medical records at random for monthly audits.

16.0.0 Statistical Considerations

Power analysis. Initial estimates based on the 2000 census data indicate that we needed to visit approximately 35% of the households in each census tract to collect the required 333 individuals. The initial sample of 3,500-4,000 participants is based on power analyses and assumptions about attrition over 20 years. For a power of 80% (the likelihood of finding an effect if it is really present), we can identify moderate effects (magnitude of the differences between groups) for various outcomes with as few as 30 participants per group at the end of the study. Working backwards by assuming 20% attrition after the baseline assessment and 15% attrition between subsequent assessments, we need approximately 3,500-4,000 participants at baseline to yield 1,680 after 20 years.

Data analyses. The study employs standard statistical software depending on the independent and dependent variables being analyzed. Data analyses include parametric and non-parametric statistics for cross-sectional comparisons applying logistic regression and mixed effects modeling as appropriate for the data. Longitudinal analyses will typically require either mixed-effects models, survival analyses, or proportional hazards depending on the data and specific outcome under study.

17.0.0 Regulatory Requirements

17.1.0 Informed Consent

Wave 4 phase 1& 2. There are three phases to the Wave 4 study. The first phase occurs in the field, at the medical research vehicles (MRVs) or in the participant's home, if they have limited mobility. If the participant has been identified as a home visit participant, consent may be obtained in the home or over the telephone. Among the preparations for their examinations on the medical research vehicles, participants are provided copies of the informed consent documents and are asked to read them. Participants are then instructed to view a consent film about the HANDLS study that explains the purpose of the study and all procedures they have previously reviewed in the informed consent documents. The HANDLS study consenter then reviews each documents with participants a final time, page by page stopping to ask if they have any questions to ensure the participant has a clear understanding of the study, the degree of risk, potential benefits, and alternatives and then provides the participant with an opportunity to ask any further questions and to consider their decision to participate in this next wave of the HANDLS study. If participants agree to take part, signatures will be obtained using an IRB approved hard copy of the informed consent document or electronically using a PC tablet. HANDLS staff provides participants with printed copies for their records and a copy is placed in the research medical record. HANDLS staff sends participants copies of all signed informed consent documents with the results from their examinations.

Alternate home visit consent procedures. This consent will be done as an oral consent, when participants are consented over the telephone. The consent form will be read to the participant verbatim. The participants will have their own copy available to review as the consenter reads it. All elements required by 45 CFR 46.116 are included, as well as required documentation of the oral consenting process using the following:

Is there anything you would like me to repeat? (Responded)	____Yes	____No
Have you understood everything I have told you? (Responded)	____Yes	____No
Do you have any questions? (Responded)	____Yes	____No
Do you agree to participate? (Responded)	____Yes	____No

Oral documentation

I have read the above informed consent over the phone to (print name of person being consented) _____ and s/he has agreed to answer the questions and participate in this research study.

*Signature recorded on last page

Print name of person reading this consent_____

Print name of witness who observed: _____

Date_____ Time: _____

Wave 4 – optional studies. Informed consent for the Circadian Rhythm Study will take place on the MRVs using in-person procedures. Informed consent for the Neuroimaging Study will take place at the UMD following guidelines set forth by their IRB and Informed consent for the Diabetes study will take place in the community and will follow procedures set forth by the University of Maryland Baltimore County IRB.

Durable Power of Attorney for Health Care Decision Making. During the wave 4 consent process participants will be asked to designate a heath care agent by completing NIH form 200-(10-00) Durable Power of Attorney for Health Care Decision Making. Participants will be informed that the designee will be able to make decisions regarding their participation in HANDLS (and any clinical care related to their participation), in the event they are unable to make their own decisions due to diminished capacity. A copy of the form will be mailed to the person they name and participants will be encouraged to discuss their known desires and values with the designee, their personal physician and their family.

17.2.0 Compensation

The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, participants are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

Participants may be reimbursed up to a total of $360.00 for participating in the HANDLS - wave 4 study. They may be paid up to $200 for participating in phase 1 ($160) and 2 ($40) of this study. If they participate in phase 3A (Ecological measurement of circadian entrainment pilot study) they will be compensated an additional $60.00. If they participate in phase 3B (Neuroimaging study) they will be compensated an additional $50.00. Finally, if a participant decides to enroll in the “Subjective Experience of Diabetes” study they will receive $50.00.

If a participant is unable to complete all of the tests they may receive a portion of that payment. They will receive payment in the form of an ATM debit card at the end of the each phase. In most cases, the ATM card will be activated by the end of the study visit day. The

participant will be instructed to take the card to an ATM machine of their choosing to withdraw payment. Written instructions regarding how to access payments will be provided. Occasionally participants are not able to complete all testing in one visit to the MRVs or some tests require repeating if there are questionable or abnormal results. We would like to be able to offer additional compensation for time and travel to return to the MRVs for return visits. The amount of compensation will vary between $20.00 and $80.00 depending on the length of time spent on the MRVs. We anticipate the return visits to be between 1-4 hours. This would include participants who never had a baseline evaluation.

17.3.0 Subject Confidentiality

HANDLS participants' confidentiality will be maintained by informing them of the following:

When results of an NIH research study are reported in medical journals or at scientific meetings, the participants will not be named and/or identified. In most cases, the NIH will not release any information about participant's research involvement without their written permission. However, if they sign a release of information form, for example for an insurance company, the HANDLS Medical Records Specialist will give the insurance company information from the medical records. Participants are informed this information might affect (either favorably or unfavorably) the willingness of the insurance company to sell them insurance.

The participants' are informed that the Privacy Act protects the confidentiality of their medical record. However, the Act allows release of some information from the medical record without permission, for example, if the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations, require it.

To help us protect privacy, we have obtained a Department of Health and Human Services Certificate of Confidentiality issued by the National Institutes of Health. With this certificate the researchers cannot be forced to disclose information that may identify participants, even by court subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The researchers will use the certificate to resist any demands for information that would identify them, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the U.S. Department of Health and Human Services that is used for auditing or program evaluation or for information that must be disclosed in order to meet federal regulations. A Certificate of Confidentiality does not prevent participants or a member of their family from voluntarily releasing information about themselves or their involvement in this research. If an insurer, employer, or other person obtains written consent to receive research information, then the researcher may not use the Certificate to withhold that information. The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without participants consent, information that would identify them as a participant in the research project under the following conditions: It does not apply to state requirements to report certain communicable diseas-

es. In addition, the study clinician may be required to report certain cases of abuse, neglect, or suicidal or homicidal intent to the appropriate authorities.

Information regarding who will have access to the data and use of personally identifiable data or private health information (PHI) are described in further detail in sections 14.0.0 (data collection and management procedures) of this protocol.

18.0.0 Participant Safety, Adverse Events, & Problem Reporting

18.1.0 Participant Safety & Intent to Treat

As the HANDLS study cohort has aged (ages 40-74 after 10th year of study), there are many participants who have developed new, more severe, or multiple chronic age-related medical conditions that require treatment. However, in this cohort participants are at times unable to regularly access needed care or are unable to be consistently compliant with medications and therapies. While participants are screened on the telephone and at times in person prior to setting their longitudinal visit appointments, participants usually do not fully relate their current medical status and level of compliance with prescribed medical regimens. Hence, we are at times confronted with participants in need of minor medical intervention. The frequency and severity of presenting symptomatology related to poorly controlled, chronic medical illness varies by participant and neighborhood demographics. Most often they report running low or out of medication because they cannot afford to fill the prescriptions to continue treatment. In those cases, once medically cleared, participants will be given a 2-4 week prescription and/or funds to fill the prescription. Once symptoms are controlled, they will return for their study visit. In these cases, with participants consent, treatment provided will be shared with the primary care physician of record. If the participant does not have a physician and is agreeable, they will be provided the available resources and assistance to obtain a primary care physician and or health insurance, if necessary.

We have determined that at times, it may be necessary to temporarily suspend the research visit for ethical and safety reasons to administer initial urgent care for treatment of significant symptoms and physical examination findings before the participant can be discharged home, to their medical provider or the local emergency department. Circumstances can become quite complicated when participants exercise their right to refuse transport to an emergency department, HANDLS staff may not be able to contact the participant's primary care provider for an urgent appointment or the participant may not have a regular physician. There are five clinical presentations that we anticipate occurring episodically at the time of the HANDLS longitudinal visit and below we outline the proposed participant safety and well-being actions that will occur in keeping with standard medical practice and ethics:

18.1.1 Poorly controlled hypertension and related medical non-compliance

Some participants will have neglected to take their medications on the day of the exam despite being told the night before to take all anti-hypertensive medications and to bring all medications to the visit. This will result in an elevated screening blood pressure reading. Participants with values <200 systolic and <100 diastolic will be asked to take their medica-

tions immediately. Their blood pressure will be monitored for reduction upon which we will allow them to remain for the study visit. If there is no reduction in blood pressure they will be advised to take their mediation as directed and referred to their primary care physician for a blood pressure check for possible modification of their regimen. They will be re-contacted in 30 days to again assess their suitability for reappointment.

Some participants will be newly diagnosed or non-compliant and have no anti-hypertensive medication. These participants will not continue their visit; they will be referred to their primary care physician for evaluation and treatment if they have a primary care physician. If there is no primary care practitioner, we will provide information about appropriate medical clinics in the vicinity in the context of their insurance status and ability to pay. Social work assistance is available on staff to assist medical staff in navigating the financial assessments. If there is no reduction in blood pressure, their visit will be terminated and they will be advised to take their mediation as directed and referred to their primary care physician for a blood pressure check for possible modification of their regimen. They will be re-contacted in 30 days to again assess their suitability for reappointment.

Participants with SBP>200mmHg and/or a DBP >110mmHg will not continue with their visit and will be sent to the closest ER. If they decline, we will document their choice with an Against Medical Advice (AMA) note in the chart signed by the participant. However, in the interest of providing best available care, we will offer the alternate of administering Clonidine and providing a prescription for standard antihypertensive medications and an appointment for follow-up at the appropriate medical venue. They will be re-contacted in 30 days to again assess their suitability for reappointment.

18.1.2 Poorly controlled diabetes mellitus and related medical non-compliance

Some participants may present with symptoms of hyperglycemia due to medical or dietary non-compliance. If there are symptoms of hyperglycemia, a finger stick will be done. For participants with elevated glucose levels >400 but < 500 as determined by glucometer monitoring will be asked to take their medications if available. If they have been non-complaint with their medications or have no medications with them, they will be treated with sliding scale regular insulin and referred back to their primary care provider for evaluation after completing their longitudinal visit. If they have no medication at home, in the interest of providing the best care possible, we will provide a prescription for their previously prescribed hypoglycemic agent or an appropriate drug if they are unable to provide the name of the drug previously taken. They will be referred to an appropriate provider for disease management. Participants with glucose >500 will be referred to the ER and their testing suspended. If they refuse ER transport, we will document their choice with an Against Medical Advice (AMA) note in the chart signed by the participant. We will treat with regular insulin and attempt to get the soonest appointment with their provider or a provider at an appropriate medical clinic. These participants will be contacted 30 days after the interrupted testing to assess their suitability for completion of their longitudinal visit.

Some participants may mistakenly take their hypoglycemic agents while they are fasting in preparation for their visit and become hypoglycemic despite being instructed the night

before the visit via telephone to bring their meds to take at the MRV after they have had their blood drawn and are ready for breakfast. Depending on their glucose level using finger stick glucometer monitoring we will administer glucotabs, oral juices or injectable glucagon. Testing will resume when patient is no longer hypoglycemic by finger stick glucometer monitoring.

18.1.3 Poorly controlled asthma/chronic obstructive pulmonary disease (COPD).

Participants at times are non-compliant with their medications or have run out of their prescriptions and present with or develop symptoms of wheezing or dyspnea. Participants with a pulse oximeter of 85-90% will receive albuterol nebulizer and/or oxygen as directed by the medical staff. If the subject's saturation does not return to 90% or greater after treatment and remains stable, the subject will be referred to the emergency room. Participants with pulse oximeter values <85% will be sent to the local emergency department. They will be recontacted in 30 days to reassess their suitability for reappointment.

18.1.4 Alcohol Withdrawal

Participants who exhibit early signs and symptoms of alcohol withdrawal during testing, will have their testing interrupted and a detailed history taken of their alcohol use. Participants with prior history of severe alcohol withdrawal will be sent to the emergency room. In some instances it may become necessary to give the participant an initial dose of short acting benzodiazepine to prevent further deterioration prior to the participant being transported to the nearest emergency room by the Emergency Medical System (EMS). Participants with no prior history of severe alcohol withdrawal will be discharged home after receiving counseling and referral to an alcoholic detox program. Participants will be re-contacted in 30 days to reassess their suitability for reappointment.

18.1.5 Seizure Disorder

Participants with a known history of seizure disorder, who have a seizure while being testing, will have their testing for the day stopped. Depending upon the situation, EMS may be activated. Participants who have a singular seizure episode with full recovery will be discharged to their primary care provider. For participants who have repeated seizure episodes, EMS will be activated and the participant will be treated with short acting benzodiazepine prior to the EMS arrival. Participants will be re-contacted in 30 days to reassess their suitability for reappointment.

For all clinical presentations in sections 18.1 to 18.1.5 above:

Participants will be asked to sign an Against Medical Advice (AMA) note if they decline EMS and or transport to an emergency room or their primary care physician's office per study clinician's advice.

If a participant's study visit is terminated due to a medical problem identified on the MRV, the study team will attempt to re-contact participant within four days to follow up and determine the outcome of treatment recommendations.

18.2.0 Adverse Events & Unanticipated Problem Reporting

Adverse events associated with HANDLS study procedures are expected to occur very infrequently. Most of the potential risks associated with study procedures (see Section 1.2) are limited to mild, transient discomforts of no clinical significance. Only clinically significant adverse events will be reported to the IRB. A clinically significant adverse event will be reported as a serious adverse event if it is life threatening, causes persistent or significant disability, leads to death, or requires medical or surgical intervention to prevent a life threatening event, persistent or significant disability or death.

Anticipated minor protocol deviations and anticipated problems or adverse events, as described in sections 18.0.0 – 18.1.5 above, will be reported to the IRB annually, as part of the continuing review process.

HANDLS staff is trained to detect and respond to clinically significant adverse events. They are expected to report clinically significant adverse events to the Principal Investigator immediately or as soon as is practical. The Principal Investigators for the HANDLS Scan and the Subjective Experience of Diabetes sub-studies are also expected to report clinically significant adverse events immediately to the NIA Principal Investigators and to follow the adverse event reporting policies of their institutions. The HANDLS principal investigator will be responsible for reporting all unanticipated clinically significant adverse events to the NIEHS IRB within 7 days of receiving notification that an event occurred.

Adverse Events, protocol deviations, unanticipated problems (UP), serious adverse events, sponsor and serious, are defined as described in NIH Human Research Protections Program (HRPP) Standard Operating Procedure (SOP) #16 entitled *Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations*. All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded. Serious unanticipated problems and serious protocol deviations will be reported to the IRB and clinical director as soon as possible but not more than 7 days after the principal investigator first learns of the event. Unanticipated problems defined as not serious will be reported to the IRB and clinical director as soon as possible but not more than 14 days after the PI first learns of the event. Unanticipated protocol deviations defined as not serious will be reported to the IRB as soon as possible but not more than 14 days after the PI first learns of the event. Serious adverse event deaths will be reported to the clinical director within 7 days after the PI learns of the event.

18.3.0 Reporting Waiver

Waiver of reporting to the IRB of anticipated minor protocol deviations and adverse events unless determined to be an Unanticipated Problem

The following anticipated minor deviations in the conduct of the protocol will not be reported to the IRB unless a procedural or protocol change is required:

We anticipate that not all HANDLS testing will be completed at each participant visit due to scheduling conflicts or time constraints either anticipated or unanticipated. As per protocol, tests/procedures may be rescheduled for another time as long as it is within the current testing period (wave), without compromising study data.

The following anticipated non-UP adverse events will not reported to the IRB unless associated with an Unanticipated Problem:

Syncope or near syncopal episodes, that occur before, during or after blood draws, hyperglycemic, hypoglycemic episodes, hypertensive urgency and hypotension that require minimal medical intervention, falls with minimal injury to the participant and do not require more than minimal medical intervention, Muscular strains or sprains which require minimal or no medical intervention, undiagnosed non-life threatening study results that require medical follow-up by primary care provider, such as critical laboratory values initiating a laboratory alert, EKG, Echocardiogram, ABI, DXA or MRI reports; and, any other non-life threatening or non-medically indicated treatment required event that occurs during the course of a participant's study visit.

19.0.0 Site and Clinical Safety Monitoring Plan

The NIA Clinical Research Protocol Office will perform routine visits to the HANDLS research site to ensure the safety and conduct of the study complies with 45 CFR 46 and NIA guidelines. Audits are performed to assure that clinical research is in compliance with FDA, DHHS domestic regulations, Clinical Practice Guidelines (GCP), and local and federal human subjects standards. An audit may be performed following an adverse event, protocol deviation or at the time of annual renewal. The Clinical Protocol Coordinator of the Clinical Research Protocol Office determines the frequency of monitoring visits. Participant records are randomly selected from the protocol to be audited. Targeted audits may also be carried out when there is specific concern regarding patient safety or data integrity. The principal investigator and clinical research coordinator of the study are notified at least three weeks in advance of the audit, and are asked to supply all research records and patient medical records for the audit.

The NIA Clinical Research Protocol Office (CRPO) staff and the Clinical Protocol Coordinator of the Clinical Research Protocol Office carry out the audits. Audit format follows the NCI guidelines for national cooperative group audits. Following intensive review of the research and medical records, a formal written report of the audit findings is sent to the principal investigator and the NIA Clinical Director. The site visits will be recorded in a visit log, by the monitor, and kept at the HANDLS research site.

The monitor will review various aspects of the study including, but not limited to:

(1) Compliance to the protocol;

(2) Review of written informed consent forms for participants enrolled;

(3) Comparison of clinic records (source documentation) to data recorded on case report forms to assure the completeness and accuracy of data collected;

(4) Continued acceptability of facilities and staff; and,

(5) Assessment of proper sample accountability, transfer and storage.

During the scheduled monitoring visits, source documentation will be made available to the monitor to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs. The Investigator (and as appropriate the research study staff) must be available to meet with the study monitor to discuss the findings from this review of Clinical Report Forms and source documents, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other study-related inquiries of the monitor.

The principal investigator will be notified of any planned visit and a date will be set that is mutually agreeable. A report will be written to document all findings, solutions and discussions. The report or a follow-up letter summarizing the contents of the report will be sent to the principal investigator. Additional follow-up will be conducted by email and telephone as needed.

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