OMB Number: 4040-0001
Expiration Date: 10/31/2019

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier**

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

2. DATE SUBMITTED | **Application Identifier**

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION **Organizational DUNS*:** 0636907050000

Legal Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: Office of Sponsored Programs
Division:
Street1*: 1720 2nd Avenue South
Street2: AB 1170
City*: BIRMINGHAM
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111

Person to be contacted on matters involving this application
Prefix: First Name*: Amanda Middle Name: Last Name*: Capps Suffix:
Position/Title: Grants and Contracts Officer
Street1*: 1720 2nd Avenue South
Street2: AB 1170
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 20549346962 Fax Number: 2059755977 Email: aos@uab.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1636005396A6

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
The Impact of Insomnia on Pain, Physical Function, and Inflammation in HIV

12. PROPOSED PROJECT
Start Date* Ending Date*
09/01/2018 08/31/2023

13. CONGRESSIONAL DISTRICTS OF APPLICANT
AL-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Burel Middle Name: R. Last Name*: Goodin Suffix:
Position/Title: Associate Professor
Organization Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: Psychology
Division: College of Arts and Sciences
Street1*: 1720 2nd Avenue South
Street2: CH 328
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352941170
Phone Number*: 205.934.8743 Fax Number: Email*: bgoodin1@uab.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$3,363,347.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$3,363,347.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Melinda Middle Name: Last Name*: Cotten Suffix:
Position/Title*: Assistant Vice President Sponsored Programs
Organization Name*: University of Alabama at Birmingham
Department: Office of Sponsored Programs
Division:
Street1*: 1720 2nd Avenue South
Street2: AB 1170
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 352940111
Phone Number*: 2059345266 Fax Number: 2059755977 Email*: ospnga@uab.edu

Signature of Authorized Representative*
Completed on submission to Grants.gov

Date Signed*
04/10/2018

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 10/31/2019

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Duns Number: 0636907050000
Street1*: 1720 2nd Avenue South
Street2: CH 328
City*: BIRMINGHAM
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 352941170
Project/Performance Site Congressional District*: AL-007

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Pittsburg
DUNS Number: 0045143600000
Street1*: 123 University Place
Street2: B21
City*: Pittsburg
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 152132303
Project/Performance Site Congressional District*: PA-014

Additional Location(s) File Name:

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ❍ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ● **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number 00005960

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ❍ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	R01_Project_Summary.pdf
8. Project Narrative*	R01_Project_Narrative.pdf
9. Bibliography & References Cited	R01_References.pdf
10.Facilities & Other Resources	R01_Fac-Resources.pdf
11.Equipment	R01_Equipment.pdf

Project Summary/Abstract

Insomnia is a sleep disorder characterized by difficulty falling asleep, staying asleep, or both, despite adequate opportunity for sleep attainment. As a result, people with insomnia may get too little sleep and/or have poor sleep quality. Insomnia is a common and debilitating sleep disorder in persons living with HIV (PLWH), with prevalence estimates ranging from 30-73%. Insomnia is increasingly viewed as a risk factor for the onset and/or worsening of pain symptoms and physical functioning deficits. Insomnia has been found to promote enhanced pain sensitivity (also known as hyperalgesia), which is critical to the etiology of pain in everyday life. This is particularly relevant for PLWH because recent evidence attests to the fact that pain symptoms are quite prevalent in the daily lives of PLWH. Whether insomnia is a risk factor for the experience of pain and poor physical functioning in PLWH is a topic that has received minimal attention to date; therefore, additional research is needed. Inflammatory processes represent an important biologic mechanism linking insomnia to pain and physical function. Insomnia promotes systemic inflammation as well as inflammatory reactivity to physical stressors like pain. Research conducted with non-HIV samples has shown that inflammation can substantially increase sensitivity to painful stimuli in the laboratory setting, as well as exacerbate pain symptoms in everyday life and physical disability. Taken together, insomnia may drive pain and physical function in PLWH through the proliferation of inflammatory mediators. There is currently a need to elucidate mechanisms and mediators of sleep disorders in PLWH, and the consequences and influences of these disturbances on other HIV-related comorbidities. Accordingly, the *overall objective* of this proposal is to investigate the impact of insomnia on pain, physical function, and inflammation in PLWH. We will accomplish our overall objective by addressing the following *specific aims*: 1) determine whether insomnia promotes increased experimental pain sensitivity and exaggerated inflammatory reactivity to painful stimuli in PLWH, and 2) determine if fluctuations in insomnia burden over time drive inflammation and pain in everyday life, and physical functioning among PLWH. These aims will be addressed using study methods developed and rigorously refined by our research team, and which have previously yielded promising preliminary results suggesting that insomnia may indeed promote pain and inflammation in PLWH. This approach is *innovative* because the impact of insomnia on pain and pain-related inflammatory processes has never before been directly examined in PLWH. Furthermore, the incorporation of objective as well as subjective measures of sleep and physical function, experimental pain testing, and a wide array of pro- and anti-inflammatory biomarkers also contributes to the innovation of this proposal. The proposed research will be *significant* because, if our hypotheses are confirmed, we will identify: 1) insomnia as a major driver of pain and physical functioning in the laboratory and in everyday life among PLWH, and 2) inflammation as an important insomnia-related mediator of pain in PLWH.

Project Narrative

Due to its prevalence and impact on quality of life and overall health, the Centers for Disease Control and Prevention has called insufficient sleep (i.e., insomnia) a “public health crisis.” Therefore, this proposal is ***relevant to public health*** because it seeks to elucidate the pain-related consequences of insomnia and underlying inflammatory mechanisms in accordance with the mission of the National Center on Sleep Disorders Research Plan, which states “mechanistic studies are needed to define the genomic, physiological, neurobiological, and developmental impact of sleep and circadian disturbances, and identify vulnerable populations”, such as persons living with HIV. Insomnia is an important and understudied comorbidity among persons living with HIV; therefore, this proposal is ***responsive to the NIH’s HIV Research Priorities,*** which identify comorbidities as high priority research topic.

Facilities and Other Resources

University of Alabama at Birmingham

The facilities at the primary performance site, the University of Alabama at Birmingham (UAB), are ideally suited to support this project. The PI, Dr. Goodin, is a recently promoted Associate Professor of Psychology in the UAB College of Arts and Sciences. He also has a secondary appointment in the Department of Anesthesiology and Perioperative Medicine, Division of Pain Medicine. Dr. Goodin is also an investigator in the UAB Center for AIDS Research (CFAR), which is directed by Dr. Michael Saag (see letter of support from Dr. Saag). The UAB CFAR provided Dr. Goodin with the Creative and Novel Ideas in HIV Research (CNIHR) pilot award as well as the study staff necessary to complete the pilot project presented as preliminary data in this application. The CFAR will continue to provide key support (e.g., access to PLWH) for the purpose of this proposal. Beyond CFAR, UAB has an incredibly diverse, rich intellectual environment, including multiple University-wide Interdisciplinary Research Centers (UWIRC; see below for further description) including the Center for Palliative and Supportive Care (CPSC), the Center for Outcomes and Effectiveness Research (COERE), and the Center for Clinical and Translational science (CCTS). Dr. Goodin is currently an investigator affiliated with each of these centers. These intellectual resources allow for frequent discussions with other NIH-funded investigators and opportunities to receive feedback on his work.

Institutional Commitment to the Principal Investigator

The PI, Dr. Goodin, came to UAB in 2012 as a tenure-track Assistant Professor. He was recently promoted to Associate Professor with tenure, and successfully obtained his first R01 award in May of 2017. Therefore, Dr. Goodin is an established investigator at this time in his career. There is substantial evidence of institutional support for Dr. Goodin as he continues to grow his program of research at UAB. Upon arrival at UAB in 2012, he received a start-up package that included computers and analytic software, ample office space within the Department of Psychology, and significant start-up funds. He was able to stock his laboratory with all of the necessary equipment to complete comprehensive experimental pain testing batteries. These resources, in combination with additional support in the form of a CFAR pilot grant, allowed him to collect the preliminary data necessary for this R01 application. Dr. Goodin's role as a CFAR investigator allows him to have ideal access to potential study participants.

Department of Psychology

As a faculty member in the Department of Psychology at UAB, the PI (Goodin) has been provided with ample laboratory space (approximately 1,000 sq feet) on the third floor of Campbell Hall, Room 323L. This laboratory space is in addition to full access to the CCTS Clinical Research Unit (described below) where the proposed study will be conducted. This laboratory space includes a common area for the completion of day-to-day study maintenance and tasks such as data entry and printing of study materials. The research assistants for this study will be able to use this laboratory space in order to contact potential participants and coordinate study schedules. Departmental support for the PI's research program is evident in that he was provided the necessary "start up" funds ($110,000) to furnish his laboratory with computers and purchase necessary equipment. Equipment that has already been purchased and is ready for use for the proposed study includes a Thermo Sensory Analyzer-II (TSA-II, Medoc, Ramat Yishai, Israel), a mechanical pressure algometer (Algomed, Medoc, Ramat Yishai, Israel), a circulating refrigerated water bath (Thermo Fisher), and weighted mechanical punctate probes (MRC Systems, Heidelburg, Germany). This equipment is currently stored at the CCTS Clinical Research Unit.

UAB 1917 HIV/AIDS Clinic

The 1917 Clinic was founded in 1988 to provide outpatient services to patients with HIV disease in the state of Alabama and surrounding states. The goals of the clinic are to provide primary, continuity patient care, social service support and case management, translational, clinical, and outcomes research (including basic science investigation, clinical trials, and cost effectiveness/clinical outcome studies), education to health care providers regarding the care of HIV-infected patients, and community outreach. Over 8,000 patients have been evaluated since the clinic opened; over 3000 of those are currently active patients. The clinic provides dental care, psychological assessment, psychiatric evaluations, and nutritional counseling.

UAB HIV Research and Informatics Service Center (RISC)

The UAB HIV Research and Informatics Service Center (RISC) provides a collaborative infrastructure to conduct HIV clinical and behavioral research through a combination of research and informatics expertise. Research core services include study coordination, recruitment and tracking, and consultation on study design, logistics, and implementation. Informatics core services include RedCap database design and management, study eligibility

queries, generation of analysis-ready datasets via integration and queries of multiple data sources, desktop support, graphic design, and health informatics consultation. The RISC team includes statisticians, data analysts, programmers, quality assurance technicians, research coordinators, research assistants, research technicians, behavioral interventionists and a grants management specialist. Several of these staff have expertise in qualitative data collection, including in-depth interviews and focus groups, and qualitative analytic methods. On average, the RISC provides informatics and/or research core services to >75 unique users supported by >40 extramural grants and contracts annually, including over 250 unique data queries for a wide range of investigators from across the UAB campus and around the world.

UAB Sleep/Wake Disorders Center

The UAB Sleep/Wake Disorders Center, continuously accredited by the American Academy of Sleep Medicine since 1986, is a 10-bed clinical and research facility with examination rooms, office space, and support staff. Convenient and accessible free parking is available for patients, research participants, and study staff. In 2016, the center evaluated more than 800 patients and performed in excess of 1750 overnight nocturnal polysomnography studies and 81 Multiple Sleep Latency Tests/Maintenance of Wakefulness Tests. These systems provide full sleep monitoring capabilities including positive airway pressure titration. The center also provides 40 actigraph watches and 8 laptops available with actigraphy software. Support through this center for actigraphy and related software matters will be available at all times during the proposed projects. Dr. Thomas has a secondary appointment with the UAB Sleep/Wake Disorders Center with office and dedicated clinical space. His behavioral sleep medicine clinic and training program is an integral part of the UAB Sleep/Wake Disorders Center and his clinical practice is comprised of patients with obstructive sleep apnea (5%), insomnia (80%), circadian rhythm sleep-wake disorders (10%), and other sleep disorders (5%). A large percentage of his patients experience chronic pain and a subset of his insomnia and sleep apnea patients have HIV.

University-wide Interdisciplinary Research Centers

A system of University-wide Interdisciplinary Research Centers (UWIRC) provides a robust framework for research and training that transcends departmental structures and clinical specialties. These trans-disciplinary centers are available to all UAB investigators and greatly enhance the research opportunities and career development of their trainees. The UWIRCs assist in coordinating thematically oriented efforts for extramural grants and contracts, in developing Center-associated core facilities and in integrating enrichment programs that are key trainee resources. Centers require sponsorship from three or more UAB schools, substantive interdisciplinary faculty involvement; provision of research infrastructure through extramural funding; contribution to the intellectual environment in order to enhance faculty and student recruitment, development, and retention; a financial base to support center and core activities; internal and external review processes to ensure quality and productivity; and leadership in the integration of research and service including community outreach or partnerships. Through a competitive review process, the Deans of sponsoring Schools and the Provost provides modest funds for research cores, pilot and feasibility studies and selective enrichment activities. By encouraging partnerships, the UWIRC program enhances collaborative research. In the most recent funding cycle, UAB committed over $4 million to 25 University-wide Inter-disciplinary Research Centers. *The following UWIRC are particularly important for the current proposal and are described in greater detail.*

UAB Center for Clinical and Translational Sciences (CCTS)

The UAB Center for Clinical and Translational Science (CCTS) supports innovative, trans-disciplinary research across the T1-T4 spectrum in order to improve human health and health care delivery. Through the CCTS Research Commons, facilities and expertise are available to assist clinical research projects including support in Biostatistics and Study Design, Clinical Services, Cores, Informatics, Pilot Programs and Project Panels. In fulfillment of the NIH-NCATS mission for these centers, funded studies are charged modest user fees for accessing the services of the CCTS. For the proposed project, the clinical resources of the CCTS including the Clinical Research Unit (CRU), a centralized Core for Specimen Processing and a Biobank/Biorepository facility for specimen management are available. It should be noted that Dr. Burel Nabors currently directs the UAB CRU (where this proposed study will be conducted), and a letter of support for the current study has been written by Dr. Nabors and included as part of this proposal. Additional information about CCTS and its resources are described below.

Information on the CCTS Partner Network

The CCTS includes Partners from the Deep South states of Alabama, Mississippi and Louisiana. Regional partners are working together to facilitate and promote unique opportunities, including drug discovery and development (with UAB, Southern Research, Auburn University and the University of South Alabama), integrative genomics (with HudsonAlpha Institute for Biotechnology), advanced magnetic resonance imaging (with Auburn University) and substantial experience with participant populations having disparities in clinical outcomes (Louisiana State University Health Science Center, the University of Mississippi Medical Center, Pennington Biomedical Research Center, the University of South Alabama, Tulane University, the University of Alabama, Tuskegee University and UAB). The PI of the proposed study (Goodin) works with faculty from UAB, University of Alabama (Tuscaloosa), Tuskegee University, and the Morehouse School of Medicine through the NIA-funded Deep South Resource Center for Minority Aging Research (RCMAR). The PI is a RCMAR Scholar and was previously awarded funding to conduct his initial work addressing racial disparities in responses to experimental pain sensitivity testing.

Clinical Research Unit (CRU): The CRU is a 15,450 square foot outpatient clinic that provides nursing staff and patient rooms to support a wide range of research. The Outpatient component of the CRU is available for all clinical encounters required for our proposed investigation. This facility has 8 patient rooms dedicated to clinical research in addition to an infusion suite and a patient waiting area. There is also a fully staffed research metabolic facility available for participant anthropometrics as well as private space to complete psychological questionnaires. For our proposed investigation, expert nursing care will be available for assisting with each study visit as well as provision of phlebotomy services for blood collection and processing. In addition, all the equipment necessary to perform the experimental pain testing procedures are stored securely in space reserved for our research study in the Outpatient component of the CRU. The PI has prior experience conducting research studies within the CRU while making use of nursing services. The PI has an excellent working relationship with the CRU nurse manager, Mrs. Jolene Lewis.

The CRU is located 6 blocks (15 minute walk) from the Campbell Hall Building in which the Department of Psychology faculty (Goodin, Younger) and research assistants will be located. In addition, the CRU is only 3 blocks from the BioMedical Research Building where co-investigator, Dr. Jessica Merlin is located. The proximity of Dr. Merlin to the CRU ensures that she could rapidly respond in the event she is needed by CRU nursing staff for any participant issue. There is free parking available for research participants at a parking deck located directly across the street from the CRU. Thus, communication among investigators, transport of specimens between the laboratory facilities, and transport of research participants to and from the parking deck will not be adversely affected by distance among the research facilities.

Specimen Processing: Dr. Jeff Edberg, a colleague of the PI, is director of the Core for Specimen Processing which is located in the CRU. This laboratory is staffed with trained research assistants and is a fully equipped research laboratory that can handle all specimen processing needs. Equipment includes multiple refrigerated centrifuges, biosafety cabinets and -80°C freezer storage. Being on the CRU unit allows for immediate specimen processing. All specimen processing needs of the proposed study will be handled in this facility. All specimens entering the laboratory are recorded in the state of the art OnCore® (Forte Research) clinical trials management system. This allows the laboratory to prepare barcoded specimen labels, track the handling of the specimens and record their storage and retrieval in an inventory database. All specimens will be recorded and tracked in OnCore® and will be made available for use when biomarker assays are to be performed.

Biobank/Biorepository: The CCTS has a laboratory facility dedicated to the long term storage and banking of human biospecimens for research purposes. This laboratory, the Biobank/Biorepository facility, is located in the Shelby Research Building and is staffed with trained research assistants and is a fully equipped research laboratory that can handle all specimen processing needs, perform sterile cell preparations and culturing, and bank specimens in an array of 5 x -80°C and 6 x cryogenic freezers. As in the Specimen Processing facility, all specimens entering the laboratory all recorded in OnCore® which allows the recording and tracking of all specimens in the lab and provides barcoded specimen labels. In addition, the storage location of every specimen is managed in an inventory database. For UPLOAD2, all specimens will be recorded and tracked in OnCore® and will be made available for use when biomarker assays are to be performed.

Human Physiology and Metabolism Core: The Physiology and Metabolism Core was designed to provide state-of-the-art assessments of human energy expenditure, substrate metabolism, body composition, body fat distribution, and bone quality; to provide cost-effective, centralized analytical services to ongoing funded and pilot research projects; to promote multi-disciplinary research and training in clinical nutrition and obesity across the UAB campus; and to offer training, advice, and instruction to students, fellows, and investigators. To this end, the Core incorporates and combines expertise and technology for assessment of hormones, immune markers, and other analytes in both humans and animal models; body composition and fat distribution; insulin sensitivity and substrate metabolism; energy expenditure; and cardiovascular function. Assessments provided by the core are direct, sophisticated, state-of-the-art measures that utilize the most current technology available. Access to these services and technologies is designed to facilitate a sophisticated, multidisciplinary, and comprehensive approach to physiology-based research and to provide common ground for collaboration and training. Technologies for the analysis of blood based immune markers and cytokines include ELISA, RIA, EIA and Mesoscale. This core is under the direction of Dr. Barbara Gower, and Dr. Gower will complete the assay of all cytokines and inflammatory markers for the proposed project. A letter of support for the current study has been written by Dr. Gower and included as part of the application.

Center for AIDS Research (CFAR)

The UAB Center for AIDS Research (CFAR) is an interdisciplinary community that promotes the health and well-being of persons living with HIV/AIDS through research, education and communication, specialty care, community programs, and informing public policy. This UWIRC, encourages and coordinates the activities of the multiple disciplines represented by the UAB schools of business, dentistry, education, engineering, health professions, medicine, nursing, optometry, public health, and the college of arts and sciences to fulfill its mission. More than 100 faculty members, including the PI of the current R01 proposal (Goodin), have appointments in the CFAR. *THE UAB CFAR provides services to support recruitment and retention, including strategies for the development and implementation of recruitment/retention techniques as well as monitoring the success of these techniques. CFAR administration has substantial experience with the recruitment and retention of diverse persons living with HIV into research studies, both in the Birmingham, AL region and nationally.* The presence of a dedicated center facilitates enrollment of women, ethnic minorities, and elders, all of whom have represent important sub-groups of persons living with HIV. The PI currently holds an appointment as a scientist with the UAB CFAR. The UAB CFAR and its affiliates represent a valuable resource for our research team in the planning and active recruitment of necessary participants for the proposed project. The UAB CFAR is dedicated to high quality interdisciplinary and translational research and training focused on the health and independence of persons living with HIV/AIDS. As such, the UAB CFAR has expressed a commitment to helping the PI complete his research and career development goals.

Center for Outcomes Effectiveness Research and Education (COERE)

The mission of the COERE is to build and maintain a program of research of improving the quality and outcome of heath care. This is accomplished through interdisciplinary teams to develop and test innovations to promote evidence-based practice, reduce inequities in care for under-served and minority populations, and improve quality of life and functional outcomes for patients. Additionally, in this process, there is a commitment to training and mentoring students, fellows and faculty in the development of methods and serving as a resource to UAB, health care systems, and related organizations to further disseminate outcomes research knowledge expertise. This University-Wide Center has a broad, multidisciplinary membership and integrates a broad scientific expertise in all areas of outcomes and effectiveness research, including quantitative methods in healthcare services research, quality measurement and improvement, patient-based outcomes measurement, epidemiological and population-based research, comparative effectiveness research, pharmaco-epidemiology, economic and decision analytic modeling, clinical data analysis and analysis of large administrative datasets and health informatics.

Equipment

The PI has previously purchased and currently possesses the following equipment, which is housed in the CCTS Clinical Research Unit.

Mechanical Pressure Pain Task. A digital, handheld, clinical grade pressure algometer will be used for the mechanical procedures (Algomed, Medoc, Ramat Yishai, Israel). This particular algometer will be used because it provides the examiner with visual feedback to maintain a consistent application rate, which is critical for maintaining high inter-examiner reliability. An application rate of 30 kPa per second will be used, as this relatively slow application rate will reduce artifact associated with reaction time. In order to assess pressure pain threshold, the examiner will apply a constant rate of pressure and the participant will be instructed to press a button when the sensation first becomes painful, at which time the device records the pressure in kilopascals (kPa).

Thermo Sensory Analyzer - II. The TSA-II (Medoc, Ramat Yishai, Israel) is a precise, computer-controlled device capable of generating and documenting responses to highly repeatable thermal stimuli, such as warmth, cold, heat-induced pain, cold-induced pain, and temporal summation. Heat stimuli will be delivered using a computer-controlled 30mm X 30mm probe. For heat pain threshold, participants will be instructed to press the button when the sensation "first becomes painful," and for tolerance the instruction will be to press the button when they "no longer feel able to tolerate the pain." This unit will also be used for the assessment of heat temporal summation. Temporal summation of heat pain will involve brief repetitive suprathreshold thermal stimuli applied to the ventral surface of the dominant forearm. For each trial, sequences of 5 consecutive heat pulses are presented and participants rate the intensity of the pain produced by each heat pulse on a 0-100 numeric rating scale. Temporal summation of heat pain is demonstrated if ratings of pain intensity following the 5th heat pulse are significantly greater than ratings of the 1st heat pulse.

Cold Pressor Pain Task. The cold pressor will serve as the conditioning stimulus for the assessment of conditioned pain modulation. It will also be used for the final aspect of the experimental pain testing battery. Participants will be instructed to immerse their dominant hands into a cold water bath maintained at 10^0C for as long as possible. The cold water temperature will be maintained (± 0.2^0C) by a refrigeration unit (Thermo Scientific). Participants will be encouraged to keep their hand immersed for at least two minutes during the cold water immersion; however, they will be told that they can discontinue at any time they choose. Unbeknownst to participants, the maximum permitted immersion time will be five minutes. They will rate the intensity of the pain experienced using the 0-100 numeric rating scale at 30 second intervals and again immediately prior to hand removal. The cold pressor task has previously been shown to be effective for eliciting a pro-inflammatory response.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Burel Middle Name R. Last Name*: Goodin Suffix:

Position/Title*: Associate Professor
Organization Name*: UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department: Psychology
Division: College of Arts and Sciences
Street1*: 1720 2nd Avenue South
Street2: CH 328
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 352941170

Phone Number*: 205.934.8743 Fax Number:

E-Mail*: bgoodin1@uab.edu

Credential, e.g., agency login: BurelGoodin1

Project Role*: PD/PI Other Project Role Category:

Degree Type: PHD Degree Year: 2010

Attach Biographical Sketch*: File Name: Goodin_bio.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Jarred Middle Name W. Last Name*: Younger Suffix:

Position/Title*: Associate Professor
Organization Name*: University of Alabama at Birmingham
Department: Psychology
Division: College of Arts and Sciences
Street1*: 1720 2nd Avenue South
Street2: Campbell Hall, Suite 233
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 352941170

Phone Number*: 205-975-5821 Fax Number:

E-Mail*: younger@uab.edu

Credential, e.g., agency login: jwyounger

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year: 2003

Attach Biographical Sketch*: File Name: Younger_bio.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Stephen Middle Name J Last Name*: Thomas Suffix:

Position/Title*: Assistant Professor
Organization Name*: University of Alabama at Birmingham
Department: Psychiatry
Division: School of Medicine
Street1*: SC 1008
Street2: 1720 2nd Ave. S.
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 352940017

Phone Number*: 205-996-0142 Fax Number:

E-Mail*: sjthomas@uab.edu

Credential, e.g., agency login: stjthomas

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD Degree Year: 2014

Attach Biographical Sketch*: File Name: Thomas_Biosketch.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Dustin Middle Name M Last Name*: Long Suffix:

Position/Title*: Assistant Professor
Organization Name*: University of Alabama at Birmingham
Department: Biostatistics
Division: School of Public Health
Street1*: RPHB 309B
Street2: 1720 2nd Ave S
City*: Birmingham
County:
State*: AL: Alabama
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 352940022

Phone Number*: 2059755955 Fax Number:

E-Mail*: dmlong@uab.edu

Credential, e.g., agency login: dustin_long

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: PHD,MS Degree Year: 2012,2006

Attach Biographical Sketch*: File Name: Long_bio.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Jessica Middle Name S Last Name*: Merlin Suffix:

Position/Title*: Visiting Associate Professor
Organization Name*: University of Pittsburg
Department: Medicine
Division: General Internal Medicine
Street1*: UPMC Montefiore Hospital
Street2: Suite W933
City*: Pittsburg
County:
State*: PA: Pennsylvania
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 152130000

Phone Number*: 215-806-1888 Fax Number:

E-Mail*: jmerlin@uab.edu

Credential, e.g., agency login: jmerlin

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MD,MBA Degree Year: 2005,2005

Attach Biographical Sketch*: File Name: Merlin_bio.pdf

Attach Current & Pending Support: File Name:

BIOGRAPHICAL SKETCH

NAME: Goodin, Burel R.

eRA COMMONS USER NAME (agency login): BurelGoodin1

POSITION TITLE: Associate Professor of Psychology and Anesthesiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Illinois College, Jacksonville, IL	B.S.	05/2002	Biology
Boston University School of Medicine, Boston, MA	M.A.	05/2004	Behavioral Medicine
University of Maryland, Baltimore County, Baltimore, MD	M.A.	08/2007	Clinical Psychology
University of Maryland, Baltimore County, Baltimore MD	Ph.D.	08/2010	Clinical Psychology
VA Connecticut Healthcare System, West Haven, CT	APA intern	08/2010	Health Psychology
University of Florida College of Dentistry, Gainesville, FL	Post-Doc	07/2012	Pain Research

A. Personal Statement

I have been trained as a clinical psychologist, with expertise in pain-related behavioral medicine. I currently serve as either principal investigator or co-investigator on several University- and NIH-funded studies examining biopsychosocial predictors of sleep disturbance, pain sensitivity, and disability in diverse populations with chronic health conditions including HIV, knee osteoarthritis, low back pain, and fibromyalgia. I have authored over 50 peer-reviewed publications, and as is detailed below, have ample experience related to pain science. My program of research is increasingly recognized nationally and internationally. Recently, I was awarded the 2017 John C. Liebeskind Early Career Investigator Award through the American Pain Society.

B. Positions and Honors

Positions and Employment

2012 - 2017 Assistant Professor, University of Alabama at Birmingham, Birmingham, AL
2017 - Associate Professor, University of Alabama at Birmingham, Birmingham, AL

Other Experience and Professional Memberships

2007 - Member, American Pain Society (APS)
2007 - Member, American Psychological Association (APA)
2010 - Member, International Association for the Study of Pain (IASP)
2015 – 2017 Chair, American Pain Society, Pain & Disparities Shared Interest Group

Honors

2010 Young Investigator Achievement Award, Pain and Disparities Special Interest Group, American Pain Society
2011 - NIH Loan Repayment Program
2013 Invited Attendee, Summer Research Institute in Geriatric Mental Health, Weill Cornell Medical College and Johns Hopkins Hospital.
2017 American Pain Society's John C. Liebeskind Early Career Achievement Award

C. Contributions to Science

1. **Use of experimental pain testing to examine pain sensitivity.** I have developed and refined methods to assess pain sensitivity and modulation (e.g., endogenous pain inhibition and facilitation) using dynamic experimental pain stimuli, also known as experimental pain testing. My previous studies have examined psychological risk and resiliency factors that are related to how people process and perceive pain. Initial

work also focused on the interactions of psychosocial and biobehavioral characteristics in relation to the experience of pain through the key pathways of stress-related hormones (neuroendocrine function) and immune function. This led to the next step in my research, which was to begin evaluating the impact of factors such as sleep disturbance and neuropeptides (e.g., oxytocin) on pain sensitivity and modulation across the adult lifespan.

a. **Goodin, B.R.**, McGuire, L., Allshouse, M., Stapleton, L., Haythornthwaite, J., Mayes, L.A., Quinn, N.B., & Edwards, R.R. (2009). Associations between catastrophizing and endogenous pain-inhibitory processes: Sex differences. *Journal of Pain*, 10(2), 180-190. PMCID: N/A.
b. **Goodin, B.R.**, Quinn, N.B., King, C.D., Page, G.G., Haythornthwaite, J.A., Edwards, R.R., Stapleton, L.M., & McGuire, L. (2011). Salivary cortisol and soluble tumor necrosis factor-α receptor II responses to multiple experimental modalities of acute pain. *Psychophysiology*, 49(1), 118-127. PMCID: PMC3235230.
c. Petrov, M.E., **Goodin, B.R.**, Cruz-Almeida, Y., King, C., Glover, T.L., Bulls, H.W., Fillingim, R.B., & Bradley, L. A. (2015). Disrupted sleep is associated with altered pain processing by sex and ethnicity in knee osteoarthritis. *Journal of Pain*, 16(5), 478-490. PMCID: PMC4424160.
d. Bulls, H.W., Freeman, E.L., Anderson, A.J.B., Robbins, M.T., Ness, T.J. & **Goodin, B.R.** (2015). Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. *Journal of Pain Research*, 29(8), 311-320. PMCID: PMC4494610.

2. **The impact of poor sleep on the experience of pain.** My research suggests that sleep and pain are related. However, many questions remain about the direction of causality in this relationship, as well as mechanisms that may account for this association. My initial research focused on characterizing the impact of poor sleep quality on pain sensitivity and mood using self-report sleep measures in non-clinical samples. Our findings demonstrated that healthy adults who reported poorer sleep quality were more sensitive to painful stimuli using quantitative sensory testing, and that the sleep-pain sensitivity relationship was mediated by factors such as pain catastrophizing and greater cortisol reactivity. More recently, this line of research has transitioned over to studying clinical samples (e.g., HIV) using micro-longitudinal study designs as well as objective (actigraphy) and subjective (diaries) measures of sleep quality. Results have suggested that patients with persistent pain complaints sleep objectively and subjectively worse than individuals without pain, and that poor sleep is a risk factor for greater clinical pain severity and functional disability. Now, there is active research in the field addressing multiple patient populations with chronic pain to study the biopsychosocial factors linking sleep and pain experiences.
    a. **Goodin, B.R.**, Fillingim, R.B., Machala, S., McGuire, L., Buenaver, L.F., Campbell, C.M., & Smith, M.T. (2011). Subjective sleep quality and ethnicity are interactively related to standard and situation-specific measures of pain catastrophizing. *Pain Medicine*, 12: 913-922. PMCID: PMC3575106.
    b. **Goodin, B.R.**, Smith, M.T., Quinn, N.B., King, C.D., & McGuire, L. (2012). Poor sleep quality and exaggerated salivary cortisol reactivity to the cold pressor task predicts greater acute pain severity in a non-clinical sample. *Biological Psychology*, 91: 36-41. PMCID: PMC3606711.
    c. Finan, P. H., **Goodin, B. R.**, & Smith, M. T. (2013). The association of sleep and pain: an update and a path forward. *Journal of Pain*, 14(12): 1539-1552. PMCID: PMC4046588.
    d. Bulls, H.W., Lynch, M.K., Petrov, M.E., Gossett, E.W., Owens, M.A., Terry, S.C., Wesson-Sides, K.M, & **Goodin, B.R.** (2017). Depressive symptoms and sleep efficiency sequentially mediate racial differences in temporal summation of mechanical pain. *Annals of Behavioral Medicine*, 51(5): 673-682. PMCID: PMC5610591.

3. **Characterization of risk factors for chronic pain in HIV.** Although individuals with HIV appear to be at increased risk for chronic pain, the factors that contribute to its development and severity remain poorly understood. A growing body of evidence derived from animal models has shown a specific physiological basis for the pathogenesis of neuropathic and non-neuropathic chronic pain associated with HIV infection. To illustrate, HIV glycoproteins such as GP120 have been found to stimulate glial cell activity that results in cascades of pro-inflammatory cytokines. In turn, inflammation intensifies the processing of painful stimuli by the peripheral/central nervous system and leads to exaggerated pain states such as hyperalgesia. Hyperalgesia refers to the phenomenon of heightened sensitivity to painful stimuli. Similar to findings from animal models, one possible risk factor for severe chronic pain in HIV-infected humans is that HIV

intensifies pain processing via promotion of inflammation, thereby resulting in heightened sensitivity to painful stimuli (i.e., hyperalgesia).

a. **Goodin, B.R.**, Owens, M.A., Yessick, L.R., Rainey, R.L., Okunbor, J.I., White, D.M., Mushatt, K.A., Harmon, O.A., Heath, S.L., & Merlin, J.S. (2017). Detectable viral load may be associated with increased pain sensitivity in persons living with HIV: preliminary findings. *Pain Medicine,* 18(12): 2289-2295. PMCID: Pending.
b. Merlin, J.S., Westfall, A.O., Heath, S.L., **Goodin, B.R.**, Stewart, J.C., Sorge, R.E., & Younger, J. (2017). IL-1B levels are associated with chronic multisite pain in people living with HIV. *Journal of Acquired Immune Deficiency Syndromes,* (E-pub ahead of print). PMCID: Pending.
c. **Goodin, B.R.**, Owens, M.A., White, D.M., Strath, L.J. Gonzalez, C. Rainey, R.L., Okunbor, J.I., Heath, S.L., Turan, J.M., & Merlin, J.S. (2018). Intersectional stigma in persons living with HIV and chronic pain: implications for depressive symptoms. *AIDS Care*, (E-pub ahead of print). PMCID: Pending.

4. **Addressing hormonal influences on the experience of pain.** As the neurobiological pathways of pain processing have been elucidated, it has become evident that there are important hormonal mechanisms that influence the experience of pain. Preliminary evidence has implicated oxytocin and vitamin D in the modulation of somatosensory transmission and pain sensitivity. I have now been involved with several studies designed to examine the effects of oxytocin and vitamin D on experimental pain sensitivity and endogenous pain inhibition as well as pain-relevant mood factors in humans. Our findings showed that endogenous pain inhibitory processes were significantly greater following administration of oxytocin compared to placebo. Similarly, negative mood and anxiety significantly decreased following administration of oxytocin but not placebo. In addition, my colleagues and I have also demonstrated that low levels of vitamin D are related to greater experimental pain sensitivity, and, among obese individuals, also to poor physical functioning and performance. Since the publication of our results, there has been an increase in studies aimed at further examining the therapeutic potential of oxytocin and vitamin D supplementation for various chronic pain conditions.

a. Glover, T.L., **Goodin, B.R.**, Horgas, A.L., Kindler, L.L., King, C.B., Sibille, K., Peloquin, C., Riley, III, J.R., Staud, R., Bradley, L.A., & Fillingim, R.B. (2012). Vitamin D, Race, and Experimental Pain Sensitivity in Older Adults with Knee Osteoarthritis. *Arthritis & Rheumatism*, 64(12), 3926-3935. PMCID: PMC3510313
b. **Goodin, B.R.**, Anderson, A.J.B., Freeman, E.L., Bulls, H.W., Robbins, M.T., & Ness, T.J. (2015). Intranasal oxytocin administration is associated with enhanced endogenous pain inhibition and reduced negative mood states. *Clinical Journal of Pain*, 31(9), 757-767. PMCID: PMC4417654.
c. **Goodin, B.R.**, Ness, T.J., & Robbins, M.T. (2015). Oxytocin–A multifunctional analgesic for chronic deep tissue pain. *Current Pharmaceutical Design*, 21(7), 906. PMCID: PMC4276444.
d. Glover, T.L., **Goodin, B.R.** King, C.D., Sibille, K.T., Herbert, M.S., Sotolongo, A., Cruz-Almeida, Y., Bartley, E.J., Bulls, H.W., Horgas, A.L., Redden, D.T., Riley, J.L., Staud, R., Fessler, B.J., Bradley, L.A., & Fillingim, R.B. (2015). A cross-sectional examination of vitamin D, obesity, and measures of pain and function in middle-aged and older adults with knee osteoarthritis. *Clinical Journal of Pain*, 31(12), 1060-1067. PMCID: PMC4494986.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/burel.goodin.1/bibliography/43136637/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01MD010441 PI: Burel Goodin 04/26/17 – 01/31/22
NIH/NIMHD
Racial and socioeconomic differences in chronic low back pain
The goal of this project is to determine whether laboratory measures of endogenous pain modulation in conjunction with biobehavioral and psychosocial factors help explain racial and socioeconomic group differences in clinical pain and disability between Blacks and Whites with chronic low back pain.
Role: Principal Investigator

R37AG033906 PI: Roger Fillingim 09/15/14 – 06/30/19
NIH/NIA
Ethnic differences in responses to painful stimuli
This project proposes to elucidate the mechanisms underlying ethnic group differences in knee osteoarthritis-related pain by directly and prospectively assessing the progression and predictors of clinical pain and disability as well as pain-related central nervous system structure and function among middle-aged and older African Americans and non-Hispanic Whites with and without knee osteoarthritis.
Role: Co-Investigator

P30 AI027767 PI: Michael Saag 06/01/16 – 05/31/18
UAB Center for Aids Research (CFAR)
Creative and Novel Research Ideas in HIV (CNIHR)
Risk Factors for Chronic Pain in HIV
In the current treatment era, individuals with HIV often experience a high burden of comorbid health conditions, including chronic pain. This study will be the first to investigate the relationships among sensitivity to painful stimuli, pro-inflammatory responses, stigma (internalized and enacted), and chronic pain severity in individuals with HIV.
Role: Principal Investigator of Pilot Award

R01AI107655 PI: Jarred Younger 10/01/14 – 9/31/19
NIH/NIAID
Daily immune monitoring in chronic fatigue syndrome
Chronic Fatigue Syndrome is a debilitating and poorly understood condition that affects over one million women in the United States. The goal with this project is to identify biological targets that will allow better treatments for chronic fatigue to be developed. This study's approach for discovering biomarkers involves monitoring fatigue and immune factor concentrations on a daily basis.
Role: Co-Investigator

Completed Support

Faculty Development Award Co-PIs: Burel Goodin, Jessica Merlin 09/01/14 – 08/31/15
UAB Faculty Senate
Characterization of pain sensitivity in HIV-infected patients.
The overall goal of this proposal is to characterize potentially important risk factors that may contribute to the development and severity of chronic pain in individuals infected with HIV. In addition to pain sensitivity, perceptions of social stigma and discrimination may be psychosocial risk factors for the experience of chronic pain in HIV-infected individuals. This study specifically examines whether perceived stigma and discrimination are associated with the experience of pain in individuals with HIV using quantitative sensory testing.

P30AG031054 PI: Burel Goodin 07/01/13 – 06/31/15
NIH/NIA: Deep South Resource Center for Minority Aging (RCMAR) Health Disparities Research Pilot Award
Racial differences in sleep and pain sensitivity across the adult lifespan.
The overall aim of this project is to gain a better understanding of whether sleep patterns and responses to painful stimulation differ according to older adults' ethnic/racial backgrounds. The study initially included healthy, community-dwelling adults free of pain, and then later transitioned to examining patients with chronic low back pain.

Future Leaders in Pain Research Award PI: Burel Goodin 01/01/13 – 5/1/14
American Pain Society
The effects of intranasal oxytocin on pain sensitivity, endogenous pain processing and mood: a randomized, placebo-controlled, crossover study.
The purpose of this research was to: 1) obtain feasibility and pilot outcome data pertaining to the impact of intranasal oxytocin, compared to placebo, on pain sensitivity and endogenous pain inhibition, and 2) examine the effects of intranasal OXT on pain-relevant mood factors and determine whether these factors are associated with pain sensitivity and endogenous pain inhibition.

Faculty Development Award Co-PIs: Burel Goodin, Tom Vetter 08/15/13 – 07/14/14

UAB Faculty Senate
Psychological predictors of longitudinal pain, function, rehabilitation, and health-related quality of life following adult spine surgery.
The primary aim of this project was to better understand which psychological protective and risk factors are most predictive of successful rehabilitation and recovery versus persistent pain and disability following adult lumbosacral spine surgery.

R21AT003250-01A1 PI: Lynanne McGuire 08/31/07 – 09/01/09
NIH/NCCAM
Neuroendocrine and immune response to hypnotic analgesia: A pilot clinical trial.
The goals of this study were to: 1) identify and refine a laboratory pain model that reliably stimulated both neuroendocrine and immunological alterations, and 2) obtain preliminary data on the effects of hypnotic suggestions on immune and neuroendocrine responses to laboratory pain.
Role: Consultant

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Younger, Jarred W

eRA COMMONS USER NAME (credential, e.g., agency login): JWYOUNGER

POSITION TITLE: Associate Professor of Psychology, Rheumatology and Anesthesiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Maryville College, Maryville, TN	B.A	06/1998	Psychology
University of Tennessee, Knoxville, TN	Ph.D.	08/2003	Experimental Psychology
Arizona State University, AZ	Postdoc	06/2005	Pain Psychology
Stanford University, Stanford	Postdoc	10/2007	Pain Management

A. Personal Statement

In this five-year R01 project, we will be testing whether insomnia is a driver of inflammation, pain, and physical function in persons living with HIV (PLWH). This project is particularly innovative because pain and inflammation will be tested in the laboratory context and in everyday life. I believe that the literature to-date supports that insomnia and pain are important, yet under-appreciated, comorbidities of PLWH. Further, insomnia has been shown to promote pain experiences via chronic inflammation. However, it remains unknown if this is the case for PLWH.

I moved from Stanford University to the University of Alabama at Birmingham in 2014, and am an Associate Professor in both the School of Medicine and College of Arts and Sciences. I direct the Neuroinflammation, Pain and Fatigue Laboratory. My work centers on discovering new methods for measuring and treating neuroinflammation in humans. I have used MRI-based techniques for over ten years, and have several ongoing projects that involve developing new neuroimaging techniques for solving complex medical problems.

My role as co-investigator on this project will include oversight of blood collection, processing, and assaying of inflammatory cytokines. I will assist with the quantification of these data as well as interpretation of the ways inflammation is related to insomnia/sleep and pain in PLWH. I have actively collaborated with Drs. Goodin and Merlin since my arrival at UAB, and I am confident in our ability to finish this project.

B. Position and Honors

Positions and Employment

2001-2003 Instructor: University of Tennessee; Knoxville, TN
2002-2003 Instructor: Maryville College; Maryville, TN
2003-2005 Postdoctoral Researcher: Arizona State University; Tempe, AZ
2005-2006 Assistant Research Scientist: Arizona State University; Tempe, AZ
2006-2007 Postdoctoral Research Fellow: Stanford University School of Medicine
2007-2010 Instructor: Stanford University School of Medicine, Stanford, CA
2010-2014 Assistant Professor, Stanford University School of Medicine, Stanford, CA
2014- Associate Professor, Departments of Psychology, Rheumatology and Anesthesiology, Director of the UAB Neuroinflammation, Pain and Fatigue Lab University of Alabama at Birmingham

Other Experience and Professional Memberships

1998 - 2016	Member, American Psychological Association
2000 - 2003	Member, Society of Behavioral Medicine
2000 - 2001	Teaching Assistant: University of Tennessee; Knoxville, Tennessee.
2001 - 2003	Graduate representative to University Faculty Senate Committee on Teaching
2002	Ad-hoc reviewer for the Psi Chi Journal for Undergraduate Research
2003 - 2005	Member of APA Div 38 (Health Psychology) Student Council (Research Committee)
2003 - 2005	Post-doctoral representative to APA Div 38 Research Committee
2004	Ad-hoc reviewer for Cognitive Therapy and Research.
2004	Ad-hoc reviewer for Psychological Bulletin
2004 - 2005	Member of Dissertation Committee: Adam McCray
2005	Ad-hoc reviewer for Journal of Personality
2006	Ad-hoc reviewer for Journal of Behavioral Medicine
2007 -	Member, American Pain Society
2008 -	Member, International Association for the Study of Pain
2009 -	Ad-hoc reviewer for the Clinical Journal of Pain, Expert Opinion on Pharmacotherapy, Journal of Pain Research, and Gender Medicine
2009	Grant reviewer for German Funding Initiative on Musculoskeletal Diseases
2009	Grant reviewer for DoD Congressionally Directed Medical Research Programs
2009 -	Member, Organization for Human Brain Mapping
2010 -	Ad-hoc reviewer for Experimental Neurology
2010 -	Editorial Board for Frontiers in Neuropsychiatric Imaging and Stimulation
2011 -	Member of Women's Health Strategic Planning Group at Stanford
2011 -	Ad-hoc reviewer for Pain Research and Treatment, Psychosomatic Medicine, Physiology and Behavior, Pain, Brain Behavior and Immunity, Clinical Psychiatry, and Pain Medicine.
2012 -	Ad-hoc reviewer for Neuropsychopharmacology, Drug and Alcohol Dependence, Biological Psychiatry, and Frontiers in Psychiatry
2012 -	Guest Editor for Pain Research and Treatment
2012 -	Pre-major advisor at Stanford
2012 -	Member of Editorial Board – Pain Medicine
2012 -	Reviewer for VA Merit Review Gulf War Illness Special Emphasis Panel
2013 -	Dissertation Committee Member for Jason Thompson
2013 -	Reviewer for NIH ME/CFS Special Emphasis Panel
2015 -	Reviewer for Department of Defense CDMRP Grant Program
2015 -	Doctoral committee advisor for Joseph Griffis, Hailey Bulls, and Vinetra King
2015 -	Scientific advisor for HealClick PCORI award

Honors

2000	Best paper by a young scientist, Soc for Clinical and Experimental Hypnosis
2002	Outstanding Graduate Research Award, University of Tennessee
2010	Department of Anesthesia Research Award, Stanford University
2011	Outstanding Research Presentation, American Academy of Pain Medicine

C. Contributions to Science

In my neuroinflammation laboratory, we utilize three major approaches – immune monitoring, neuroimaging, and pharmaceutical – to reach our research goals. Because this R01 proposal is primarily an inflammation project, I will focus on my contributions to science that involve the use of human blood assays for quantification of cytokines and chemokines. I have used ELISA and Multiplex techniques to assay cytokines in studies exploring causes of chronic diseases in the central nervous system. I also have strong experience in structural MRI, functional MRI, longitudinal analyses, connectivity analyses, machine learning classification and pharmacologic fMRI. More recently, I have led projects addressing daily fluctuations in immune functioning (including inflammation) in an effort to determine whether these fluctuations explain variability in pain and fatigue symptoms. At present, my group is working on several neuroimaging advancements that will more directly assess neuroinflammation in humans.

1. Atypical inflammation is a likely cause of chronic pain and fatigue

Most of my research involves chronic fatigue syndrome, fibromyalgia, and Gulf War illness. I believe these three conditions involve low-level systemic inflammation, with pain and fatigue driven by microglia and astrocyte activation in the brain. By employing a unique, daily immune monitoring paradigm, I have demonstrated that fatigue and pain are strongly tied to specific inflammatory markers in peripheral blood. I have also shown that drugs with known microglia-modulating properties are highly effective in treating chronic pain. My next steps in this line of research involve extending the analyses to the central nervous system.

● Parkitny L, **Younger J.** Reduced pro-inflammatory cytokines after eight weeks of low-dose naltrexone for fibromyalgia. *Biomedicines*, 5: 2. PMID: 28536359

● Parkitny L, Middleton S, Baker K, **Younger J.** (2015). Evidence for abnormal cytokine expression in Gulf War Illness: A preliminary analysis of daily immune monitoring data. *BMC Immunology,* 16: 57. PMID: 26420016.

● Stringer EA, Baker KS, Carroll IR, Montoya JG, Chu L, Maecker HT, **Younger J**. (2013). Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: Evidence of inflammatory pathology. *Journal of Translational Medicine,* 11: 93. PMID: 23570606.

● **Younger J**, Noor N, McCue R, Mackey S. (2013). Low-dose naltrexone for the treatment of fibromyalgia: A small, randomized trial on daily pain. *Arthritis & Rheumatism*, 65(2), 529-38. PMID: 23359310.

2. Neuroimaging methods can reveal pathophysiological mechanisms in chronic pain and fatigue

Magnetic resonance imaging has given us the ability to examine the central nervous system correlates of chronic pain and fatigue disorders. Such information may guide the development of new treatments that specifically target pathophysiological mechanisms. I have used structural and functional analytic techniques to investigate complex chronic conditions such as complex regional pain syndrome (CRPS), low back pain, and chronic temporomandibular pain. I have also worked on several projects developing an objective measure of pain severity, using neuroimaging data.

● Ung H, Brown JE, Johnson KA, **Younger J**, Hush J, Mackey S. Multivariate classification of structural MRI data detects chronic low back pain. Cereb Cortex. 2014 Apr;24(4):1037-44. doi: 10.1093/cercor/bhs378. Epub 2012 Dec 17. PubMed PMID: 23246778; PubMed Central PMCID: PMC3948494.

● Barad MJ, Ueno T, **Younger J**, Chatterjee N, Mackey S. Complex regional pain syndrome is associated with structural abnormalities in pain-related regions of the human brain. J Pain. 2014 Feb;15(2):197-203. doi: 10.1016/j.jpain.2013.10.011. Epub 2013 Nov 7. PubMed PMID: 24212070.

● Brown JE, Chatterjee N, **Younger J**, Mackey S. Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation. PLoS One. 2011;6(9):e24124. doi: 10.1371/journal.pone.0024124. Epub 2011 Sep 13. PubMed PMID: 21931652;

● **Younger J**, Shen YF, Goddard G, Mackey SC. Chronic myofascial temporomandibular pain is associated with neural abnormalities in the trigeminal and limbic systems. Pain. 2010 May;149(2):222-8. doi: 10.1016/j.pain.2010.01.006. Epub 2010 Mar 16. PubMed PMID: 20236763; PMC2860657.

3. Neuroimaging can be used to understand the neurobiological mechanisms of treatments

I am highly interested in using neuroimaging to better understand beneficial and adverse treatment effects. Effective treatments for chronic pain and fatigue will very likely target central nervous system targets, and biomarkers for clinical response are needed. My work was the first to show that opioid analgesics rapidly change the human brain. These changes are located in mesolimbic reward areas such as the amygdala and occur within a month of starting opioid use. The degree of volume loss in these regions also predicts drug craving after stopping opioids. This information may therefore be helpful in discovering why some people are more susceptible than others to opioid addiction. I have also used functional neuroimaging to show how strong rewarding experiences such as love reduce experimental pain. My results suggest that reward system activation in the nucleus accumbens results in descending pain modulation at the spinal level. This information can help us develop pain modulation techniques such as real-time functional magnetic resonance biofeedback.

● Lin J, Chu LF, Stringer EA, Baker K, Sayyid Z, Sun J, **Younger J.** One month of oral morphine decreases gray matter in the right amygdala of individuals with low back pain: Confirmation of previously reported magnetic resonance imaging results. Pain Med, in press.

● Chu LF, Lin JC, Clemenson A, Encisco E, Sun J, Hoang D, Alva H, Erlendson M, Clark JD, **Younger J**. Acute opioid withdrawal is associated with increased neural activity in reward-processing centers in healthy men: A functional magnetic resonance imaging study. Drug Alcohol Depend. 2015 May 27. pii: S0376-8716(15)00215-X. doi: 10.1016/j.drugalcdep.2015.04.019. [Epub ahead of print] PubMed PMID: 26059463.

● **Younger J**, Chu LF, D'Arcy NT, Trott KE, Jastrzab LE, Mackey SC. Prescription opioid analgesics rapidly change the human brain. Pain. 2011 Aug;152(8):1803-10. doi: 10.1016/j.pain.2011.03.028. Epub 2011 Apr 30. PubMed PMID: 21531077; PubMed Central PMCID: PMC3138838.

● **Younger J**, Aron A, Parke S, Chatterjee N, Mackey S. Viewing pictures of a romantic partner reduces experimental pain: involvement of neural reward systems. PLoS One. 2010 Oct 13;5(10):e13309. doi: 10.1371/journal.pone.0013309. PubMed PMID: 20967200; PubMed Central PMCID: PMC2954158.

Complete List of Published Work:
An updated publication list can be found at the publically-available ResearchGate link below.
http://www.researchgate.net/profile/Jarred_Younger/publications

D. Research Support

Ongoing Research Support

GW110044 Younger (PI) 07/01/14 – 02/29/18
Identifying Immune Drivers of Gulf War Illness Using a Novel Daily Sampling Approach
The major goal of this project is to screen for inflammatory markers that are characteristic of Gulf War Illness.
Role: PI

GW130015 Younger (PI) 10/1/14 – 05/30/18
Treating Gulf War Illness with Novel Anti-Inflammatories: A Screening of Botanical Microglia Modulators
The major goal of this project is to screen nine botanical anti-inflammatories for treatment of Gulf War Illness.
Role: PI

1R01AI107655-01A1 Younger (PI) 07/01/14 – 06/30/19
Daily Immune Monitoring in Chronic Fatigue Syndrome
This project screens blood samples for inflammatory agents that drive symptom in women with chronic fatigue.
Role: PI

Solve ME/CFS – Ramsay Award Younger (PI) 03/01/17 – 02/28/18
Advanced non-invasive analysis in ME/CFS diagnosis and treatment decisions
The goal of this project is to develop neuroimaging scans that can differentiate ME/CFS patients from controls.
Role: PI

Rheumatology Research Foundation 05/01/16 – 12/1/17
Non-invasive measurement of brain inflammation in rheumatoid arthritis.
We are exploring MR-based markers of neuroinflammation in RA-associated fatigue.
Role: PI

Functional Neurorecovery Center 08/01/17 – 08/01/18
This project assesses overlap of MRS neuroinflammatory markers with structural images of brain trauma.
Assessing brain inflammation in traumatic brain injury
Role: PI

Completed Research Support in Last 3 years

Neuroimaging Program Development and Research Acceleration Award Younger (PI) 11/15-10/16
Functional Diffusion Tensor Imaging (fDTI): A Novel Method to Measure Neural Connectivity in the Spinal Cord.
The major goal is to develop a method for imaging task-related activity in white matter tracts in the spinal cord.
Role:PI

Fetzer Foundation Award Younger (PI) 02/09/15 – 08/31/16
Moral Elevation and the Brain
This project determines if oxytocin via evoked feelings of altruism can reduce the experience of pain.
Role: PI

IASP International Trainee Fellowship Younger (PI) 07/14/14 – 07/13/15
The goal of this international trainee fellowship is to explore immune drivers of chronic pain and fatigue.
Role: Mentor

HHSN268201100003C Stefanick (PI) 10/2010-9/2015
This project examines the large WHI database for important health-related trends in post-menopausal women.
Role: Investigator

P01 AT006651 Mackey (PD) 09/01/11 – 05/31/16
Stanford CAM Center for Chronic Back Pain
This clinical trial tests real-time functional magnetic resonance feedback training (rtfMRI) in low back pain.

Sex/Gender-Specific Brain Risks for Prescription Opioids in Chronic Low Back Pain 11/2013 – 11/2015
The goal is to explore gender-specific differences in brain morphometry in predicting opioid abuse.
Role: Co-Investigator

1R00DA023609-03 Younger (PI) 7/01/2010 - 6/30/2013
Mechanisms of Opioid-Induced Hyperalgesia in Pain Patients: Examination via fMRI.
The goal of this project was to determine brain and health changes caused by opioids.
Role: PI

Immune Screening in Fibromyalgia Patients Younger (PI) 4/1/2012-3/31/2013
The goal was to develop a preliminary blood test to diagnosis of fibromyalgia.
Role: PI

Identifying inflammatory drivers of chronic fatigue via daily immune and symptom sampling
Identify chronic fatigue biomarkers Younger (PI) 5/1/2011-4/30/2012
The goal was to identify blood biomarkers for diagnosing chronic fatigue syndrome.
Role: PI.

Peripheral Biomarkers of Opioid-Induced Hyperalgesia, Cognitive Dysfunction, and Drug Craving
Inflammatory serum markers for opioids Younger (PI) 9/1/2010 – 8/31/2013
The goal was to assess serum markers of inflammation that predicted adverse opioid events.
Role: PI

Microglia Modulators for Chronic Multisymptom Illnesses
Treatments designed for chronic pain and fatigue Younger (PI) 07/01/2010-06/30/2013
The goal was to design novel, microglia-based treatments for chronic pain and fatigue disorders.
Role: PI

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Stephen Justin Thomas

eRA COMMONS USER NAME (credential, e.g., agency login): STJTHOMAS

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama at Birmingham, Birmingham, AL	B.S.	12/2004	Biology
University of Alabama at Birmingham, Birmingham, AL	B.S.	05/2008	Psychology
University of Alabama, Tuscaloosa, AL	M.A.	05/2011	Clinical Psychology (Sleep)
University of Alabama, Tuscaloosa, AL	Ph.D.	06/2014	Clinical Psychology (Sleep)
University of Florida, Gainesville, FL	Intern	06/2014	Health Psychology (Sleep & Pain)
University of Alabama at Birmingham, Birmingham, AL	Post-doc	06/2017	Hypertension and Sleep Research

A. Personal Statement

I am a clinical health psychologist and have spent the past 10 years actively engaged in clinical research focused on sleep and associated mental and physical health outcomes. Most recently, as a postdoctoral research fellow in an American Heart Association-funded Hypertension Strategically Focused Research Network (2015-2017), I conducted translational research on the effect of dietary sodium intake on circadian clock genes, inflammatory cytokines, obstructive sleep apnea, and diurnal blood pressure in blacks compared with whites. I remain on this grant as a co-investigator. I have also conducted population-level analyses on racial disparities in sleep and hypertension using data from both the Coronary Artery Risk Development in Young Adults (CARDIA) study and the Jackson Heart Study. In addition to these research pursuits, I have completed two different accredited clinical fellowships in behavioral sleep medicine (BSM), one of which was conducted as part of the sleep and pain research laboratories of Drs. Christina McCrae and Michael Robinson at the University of Florida. I have developed a BSM Clinic and Training Program in affiliation with the UAB Sleep/Wake Disorders Center where I provide a range of BSM services, including assessment and treatment of insomnia, and supervise trainees seeking clinical and research experiences in BSM. In this clinic, I see a relatively large number of patients with co-morbid insomnia and chronic pain. I believe this background positions me extremely well to serve as a co-investigator on this project investigating the impact of insomnia on pain and inflammation in people living with HIV.

My selected publications below underscore the diversity of my research experiences within the scope of sleep medicine and associated mental and physical health outcomes. Furthermore, my training as a clinical health psychologist and BSM specialist allows me to contribute a unique perspective of human behavior to sleep, sleep disorders, and health outcomes research.

Thomas SJ, Booth JN 3rd, Bromfield SG, et al. Clinical and ambulatory blood pressure in a population-based sample of African Americans: the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:204-212. doi: 10.1016/j.jash.2017.02.001.

Lichstein KL, **Thomas SJ**, Woosley JA, Geyer JD. Co-occurring insomnia and obstructive sleep apnea. *Sleep Med.* 2013;14:824-829.

Thomas SJ, Lichstein KL, Taylor DJ, et al. Epidemiology of bedtime, arising time, and time in bed: analysis of age, gender, and ethnicity. *Behav Sleep Med*. 2011;12:169-182. doi:10.1080/15402002.2013.778202.

Dillon HA, **Thomas SJ**, Lichstein KL. Cognitive arousal and sleep complaints in chronic pain. *Cog Ther and Res*. 2012;36:149-155.

B. Positions and Honors

Positions and Employment

1997-2007	Sleep Technologist, Sleep/Wake Disorders Center, University of Alabama at Birmingham, Birmingham, AL
2007-2010	Research Assistant, Vascular Biology and Hypertension Program, Department of Medicine, University of Alabama, Birmingham, AL
2008-2010	Graduate Research Assistant, Sleep Research Project, Department of Psychology, University of Alabama, Tuscaloosa, AL
2010-2011	Behavioral Sleep Medicine Fellow, Alabama Sleep Medicine and Neurology, Northport Alabama
2011-2012	Graduate Teaching Assistant & Instructor, Department of Psychology, University of Alabama
2012-2013	Graduate Research Assistant, TIDE grant, Department of Psychology, University of Alabama, Tuscaloosa, AL
2013-2014	Clinical Psychology Intern, Department of Clinical Psychology, University of Florida Health Sciences Center, Gainesville, FL
2014-2015	Clinical Psychologist, Birmingham VA Medical Center, Birmingham, AL
2015-2017	Postdoctoral Scholar, Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL
2017-	Assistant Professor, Divisions of Behavioral Neurobiology and Adult Psychiatry, Department of Psychiatry, University of Alabama at Birmingham, Birmingham, AL

Professional License and Certification

2015-present	Licensed Clinical Psychologist, Alabama (#1492)

Other Experiences and Professional Memberships

2001	Dement Fellowship in Sleep and Chronobiology, Sleep and Chronobiology Research Laboratory, Department of Psychiatry and Human Behavior, Alpert School of Medicine, Providence, RI
2001-	Member, Sleep Research Society
2009-2011	Trainee Symposium Series Subcommittee, Trainee Education Advisory Committee, Sleep Research Society
2010-	Founding Member, Society of Behavioral Sleep Medicine
2010-	Member, American Psychological Association
2012-	Member, Association of Behavioral and Cognitive Therapies
2013-	Member, American Academy of Sleep Medicine
2015-	Member, American Heart Association

Honors

2008	Ost Undergraduate Research Award, University of Alabama at Birmingham
2009	Research Travel Award, Graduate Student Association, University of Alabama
2009-2011	Research Travel Award, Department of Psychology, University of Alabama
2010-2011	Research Travel Award, Graduate School, University of Alabama
2011	Meritorious Abstract Travel Award, Sleep Research Society

2014 Research Travel Award, Department of Psychology, University of Alabama
2014 Research Travel Award, Graduate School, University of Alabama
2016 Young Investigator Research Forum, American Academy of Sleep Medicine
2016 Sleep Research Network Travel Award, Sleep Research Network

C. Contribution to Science

1. Poor/insufficient sleep and sleep disorders are associated with cardiovascular morbidity and mortality. However, the mechanisms underlying the role of sleep in cardiovascular outcomes are not fully understood. Furthermore, treatment of sleep disorders has not consistently been found to improve cardiovascular outcomes. For example, despite the strong relationship between obstructive sleep apnea (OSA) and hypertension, treatment of OSA with continuous positive airway pressure has only produced modest and inconsistent improvements in blood pressure. Therefore, we have sought to better understand potential mechanisms underlying the relationship between sleep and hypertension and, in particular, those that might explain the modest effect of treatment of sleep disorders on cardiovascular outcomes such as hypertension. Our findings suggest that chronic fluid retention and plasma aldosterone concentration are both related to severity of OSA and the former may mediate the relationship between OSA and resistant hypertension. These results may guide treatments aimed at improving both sleep and cardiovascular outcomes. I served as a co-investigator in both of these studies.

Thomas SJ, Booth JN 3rd, Bromfield SG, et al. Clinical and ambulatory blood pressure in a population-based sample of African Americans; the Jackson Heart Study. *J Am Soc Hypertens*. 2017;11:204-212. doi: 10.1016/j.jash.2017.02.001.

Thomas SJ, Calhoun DA. Sleep, insomnia, and hypertension: current findings and future directions. *J Am Soc Hypertens*. 2017;11:122-129. doi: 10.1016/j.jash.2016.11.008.

Gaddam K, Pimenta E, **Thomas SJ**, et al. Spironolactone reduces severity of obstructive sleep apnea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens*, 2010;24:532-537.

Gonzaga CC, Gaddam KK, Ahmed MI, **et al**. Severity of obstructive sleep apnea is related to aldosterone status in subjects with resistant hypertension. *J Clin Sleep Med.* 2010;6:363-368.

2. The field of behavioral sleep medicine has been instrumental in identifying the role that cognitive and behavioral factors play in the initiation and maintenance of sleep disorders, as well as developing evidence-based cognitive-behavioral treatments for these sleep disorders. However, the application of these treatments has not been investigated in all populations. Furthermore, the impact of cognitive-behavioral treatments on comorbid mental and physical health conditions has not been fully examined. Therefore, we have sought to explore the effect of sleep and sleep disorder treatments on health outcomes. Our findings below have demonstrated that insomnia and OSA commonly co-occur, poor sleep frequently is associated with both mental and physical health complaints, and cognitive-behavioral treatments are effective in a variety of populations (e.g., older adults) and delivery modalities (e.g., telehealth). I have been the principal investigator on one study and co-investigator on all of the other studies below.

Lichstein KL, Scogin FR, **Thomas SJ**, et al. Telehealth cognitive behavior therapy for co-occurring insomnia and depression symptoms in older adults. *J Clin Psych*. 2013;69:1056-1065.

Lichstein KL, **Thomas SJ**, Woosley JA, Geyer JD. Co-occurring insomnia and obstructive sleep apnea. *Sleep Med.* 2013;14:824-829.

Thomas SJ, Lichstein KL, Taylor DJ, et al. Epidemiology of bedtime, arising time, and time in bed: analysis of age, gender, and ethnicity. *Behav Sleep Med*. 2011;12:169-182. DOI:10.1080/15402002.2013.778202.

Dillon HA, **Thomas SJ**, Lichstein KL. Cognitive arousal and sleep complaints in chronic pain. *Cog Ther and Res*. 2012;36:149-155.

Complete List of Peer-Reviewed, Data-Based Publications from My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/?reload=addfrompubmed&sortby=pac&groupby=citation_type

D. Research Support

Ongoing Research Support

AHA Hypertension Strategically Focused Research Network Calhoun (PI) 06/29/2015-
Mechanisms of Nocturnal Hypertension and Non-Dipping Blood Pressure Pattern
The aim of this study is to investigate the role of sodium intake on sleep, nocturnal hypertension, and non-dipping blood pressure pattern through a high/low salt diet cross-over study in participants who have been identified as having nocturnal hypertension by ambulatory blood pressure monitoring.
Role: Postdoctoral Scholar (former) and Co-Investigator (current)

Completed Research Support

University of Alabama Graduate School Thomas, SJ (PI) 06/2012 – 6/2013
A survey of sleep disorders in college students: A study of prevalence and outcomes
The aim of this study was to identify sleep complaints, sleep disorders, and mental/physical health outcomes, as well as the association between sleep complaints and disorders and academic performance. This study was novel in that it incorporated a clinical interview to improve diagnostic accuracy in students who presented with any sleep complaints.
Role: Principal Investigator

National Institutes of Health, National Institute of Mental HealthLichstein, KL (PI) 2010 – 2015
Treatment of insomnia and depression in elders
The aim of this study was to provide a manualized cognitive behavioral treatment for insomnia in depression in older adults via telemedicine to determine its effect on both symptoms of insomnia and depression.
Role: Graduate Research Assistant

National Institutes of Health, National Institute on Drug Abuse Lichstein, KL (PI) 2002 – 2010
Treating addiction to sleep medication
The aim of this study was to examine the effect of three treatment arms on sleep outcomes in the context of hypnotic medication withdrawal: medication withdrawal only, medication withdrawal and cognitive behavioral therapy for insomnia, and medication withdrawal and sham biofeedback.
Role: Graduate Research Assistant

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH
DO NOT EXCEED FIVE PAGES.

NAME: Long, Dustin M

eRA COMMONS USER NAME (credential, e.g., agency login): DUSTIN_LONG

POSITION TITLE: Assistant Professor of Biostatistics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tennessee Wesleyan College, Athens, TN	BS	05/2001	Mathematics
Tennessee Tech University, Cookeville, TN	MS	05/2006	Mathematics
University Of North Carolina at Chapel Hill, Chapel Hill, NC	PhD	12/2012	Biostatistics

A. Personal Statement

My role as a co-investigator is to assist with the study design and oversee all statistical analysis. During my training at the University of North Carolina at Chapel Hill, I assisted several HIV investigators as a graduate assistant under Dr. Michael Hudgens. Additionally, my dissertation developed several biostatistical methods pertaining to HIV studies. Since joining the University of Alabama at Birmingham, I began working with the Center for Aids Research (CFAR) as a biostatistician, providing biostatistical support to all CFAR member or to those researching diseases and behaviors related to HIV. In that capacity, Dr. Goodin and I have worked together on several projects with multiple manuscripts either under review or in preparation. This experience, along with my general consulting experience, makes me an excellent choice to be a part of Dr. Goodin's team.

B. Positions and Honors

Positions and Employment

2016-Present Assistant Professor, Biostatistics, University of Alabama at Birmingham, Birmingham, AL
2012-2016 Assistant Professor, Department of Biostatistics, West Virginia University, Morgantown, WV

Other Experience and Professional Memberships

2006-2010 NIEHS Pre-Doctoral Trainee in Environmental Biostatistics (NIEHS grant T32-ES07018)
2008-present Member of the American Statistical Association
2010-present Eastern North American Region of the International Biometric Society

Honors

2013 Distinguished Student Paper Award, Eastern North American Region of the International Biometrics Society

2010 Tanner Award for Excellence in Undergraduate Education by a Graduate Teaching Assistants, University of North Carolina, Chapel Hill, NC

C. Contribution to Science

1. My doctoral dissertation was largely focused on causal inference in the presence of a post randomization variable with effected the outcomes. Principal stratification is one method to allow for causal effect estimates when these issues arise. Two publications dealt with this issue directly with regards to prevention of mother-to-child transmission of HIV via breastmilk using data from the Breastfeeding, Antiretrovirals, and Nutrition Study, first in a competing risk setting and secondly, the use of a baseline covariate to improve estimation of the causal effect. The third used principal stratification to improve determination surrogates of protection in repeated low dose studies of HIV which typically take place in monkeys.

a. **Long DM**, Hudgens MG. (2012). Comparing competing risk outcomes within principal strata, with application to studies of mother-to-child transmission of HIV. Stat Med, 31(27):3406-18. PMID:22927321.
b. **Long DM**, Hudgens MG. Sharpening bounds on principal effects with covariates. Biometrics. 2013 Dec;69(4):812-9. doi: 10.1111/biom.12103. Epub 2013 Nov 18. PubMed PMID: 24245800; PubMed Central PMCID: PMC4086842.
c. **Long DM**, Hudgens MG, Wu CD. Surrogates of protection in repeated low-dose challenge experiments. Stat Med. 2015 May 10;34(10):1747-60. doi: 10.1002/sim.6436. Epub 2015 Jan 28. PubMed PMID: 25628249; PubMed Central PMCID: PMC4390486.

2. As a biostatistician, collaboration with researchers is key to increasing the biostatistical sophistication at your home institution. At West Virginia University, I have had the opportunity, via our CTSI and Prevention Research Center, to collaborate with various researchers, in both an academic and clinical setting. For example, I have had several publications with Dr. Jorge Con, a trauma surgeon. These collaborations help to increase and improve the research profile of our university while adding higher quality publications.

a. Con J, **Long D**, Sasala E, Khan U, Knight J, Schaefer G, Wilson A. “Secondary overtriage in a statewide rural trauma system.” J Surg Res. 2015 Apr 2. pii: S0022-4804(15)00336-4. doi: 10.1016/j.jss.2015.03.077. [Epub ahead of print] PubMed PMID: 25959835.
b. Croston, T.L., Dharendra T., Holden A.A., Tveter KJ, Lewis S.E., Shepherd D.L., Nichols C.E., **Long DM**, Olfert IM, Jaqannathan R, Hollander JM. (2014) "Functional Deficiencies of Subsarcolemmal Mitochondria in the Type 2 Diabetic Human Heart." American Journal of Physiology-Heart and Circulatory Physiology. PMID: 24778174.
c. Schmidt, RJ, Weaner, BB, **Long DM.** (2014) “The Power of Advance Care Planning in Promoting Hospice and Out-of-Hospital Death in a Dialysis Unit.” Journal of Palliative Medicine. PMID: 25006866
d. Con, J., Friese, R.S., **Long, DM**, Zangbar, B, O’Keeffe, T, Joseph, B, Rhee, P, Tang, AL. (2014) “Falls from ladders: age matters more than height,” Journal of Surgical Research, Volume 191, Issue 2, October 2014, PMID: 25066188

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/dustin.long.1/bibliography/47446290/public/?sort=date&direction=ascending

D. Research Support

Ongoing Support:

P30-AI027767-29 Saag (PI) 10/01/16-05/31/19
UAB Center for AIDS Research
In support of interdisciplinary AIDS research efforts, CFAR clinical and basic science studies through the use of shared facilities and services to translate fundamental knowledge about AIDS and its related disorders into clinical treatment and prevention programs

Role: Co-Investigator

1U48DP005004 Dino (PI) 9/30/14-9/29/19
WV Prevention Research Center
Collaborate with partners to foster, conduct, and translate prevention research into effective and culturally-competent prevention strategies.
Role: Co-Investigator

1U58DP005488-01 Fitch (PI) 10/01/14-9/29/17
The West Virginia Healthy Children Project
The project aims to increase healthy eating and physical activity behaviors of families with young children
Role: Supporting

15SFRN23900002 Calhoun (PI) 04/01/15 – 03/31/19
Mechanisms of Nocturnal Hypertension and Non-Dipping Blood Pressure
The overall objective of this project is to test the hypothesis that high dietary sodium is an important cause of abnormal BP patterns, including nocturnal hypertension and nondipping BP.
Role: Supporting

Completed Support:

1U48DP005004 Dino (PI) 9/30/2009-9/29/2014
WV Prevention Research Center
Collaborate with partners to foster, conduct, and translate prevention research into effective and culturally-competent prevention strategies.
Role: Co-Investigator

U54 GM104942 Hodder (PI) 08/31/2012-06/26/2016
West Virginia IDEA-CTR
The major goals of the project are to expand the infrastructure for, and practice of, clinical and translational research to a level competitive for a Clinical and Translational Science Award (CTSA).
Role: Co-Investigator

OMB No. 0925-0001 and 0925-0002 (Rev. 09/17 Approved Through 03/31/2020)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Merlin, Jessica S

eRA COMMONS USER NAME (credential, e.g., agency login): JMERLIN

POSITION TITLE: Visiting Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Carnegie Mellon University, Pittsburgh, PA	BS	06/2000	Biology
University of Pennsylvania, Philadelphia, PA	MD	05/2005	N/A
University of Pennsylvania, Philadelphia, PA	MBA	05/2005	Health Care Management
University of Alabama at Birmingham, School of Public Health, Birmingham, AL	PHD	12/2017	Health Education/Promotion, Department of Health Behavior
Hospital of the University of Pennsylvania, Philadelphia, PA	Resident	06/2008	Internal Medicine
Hospital of the University of Pennsylvania, Philadelphia, PA	Fellow	06/2010	Infectious Diseases
Mt. Sinai School of Medicine, NY, NY	Fellow	06/2011	Palliative Care
National Institutes of Health	NIH training grant	08/2014	UAB K12 in Patient Centered Outcomes Research
National Institutes of Health	NIH training grant	present	K23 Career Development Award

A. Personal Statement

I am an Associate Professor of Medicine and a co-Investigator on the proposed project. I recently relocated from the University of Alabama at Birmingham (UAB) to the University of Pittsburgh; however, I remain actively engaged in research projects at UAB. I am extremely familiar with the UAB 1917 HIV clinic, its patients, and how it operates. I have developed expertise in HIV and chronic pain over the past 10 years, beginning with my infectious diseases and palliative care fellowships. I am one of three people in the US fellowship trained in both of these disciplines. I began working on HIV and chronic pain as an infectious diseases fellow, and published my first paper on this topic in 2011. My research in this area has included the clinical epidemiology of chronic pain in individuals with HIV in the Center for AIDS Research Network of Integrated Clinical Systems Database, psychometric work on a new Brief Chronic Pain Questionnaire used to identify chronic pain in individuals with HIV, and qualitative work on the chronic pain experience in this population.

During this time, I cultivated a strong interest in developing behavioral interventions for chronic pain that are tailored to individuals with HIV. This led to a successful K23 application on this topic. I am currently in year 3 of my K23. The overall objective of my K23 is to develop and pilot test a behavioral intervention for chronic pain tailored to people living with HIV. I led the formative behavioral intervention development work, which included qualitative inquiry and a rigorous process of intervention mapping to incorporate Social Cognitive Theory into all aspects of the intervention. The resulting intervention is based on a Pain Self-Management approach, and includes a novel peer co-led group component as well as one-on-one sessions led by staff interventionists. In the pilot trial, we found the intervention to be feasible, acceptable, and show preliminary evidence of efficacy. As part of this Career Development Award, I completed a PhD in Health Behavior at UAB that has allowed me to lead this rigorous development and testing process.

As a result of this initial work, I have achieved national recognition in my field. I received an American Academy of Hospice and Palliative Medicine Young Investigator Award and an award for being an Inspirational Leader Under 40; developed a module on HIV and chronic pain for the NIH Pain Consortium Center of

Excellence in Pain Education; serve on the Infectious Diseases Society of America's HIV and Pain Guidelines Panel; and am a Core Faculty member of the IAS-USA, in which I lecture on HIV and chronic pain. My scientific background in HIV and chronic pain, additional training obtained during my K awards, and clinical expertise uniquely positions me to be a co-investigator on the proposed project.

1. Merlin JS, Young SR, Johnson MO, Saag M, Demonte W, Modi R, Shurbaji S, Anderson WA, Kerns R, Bair MJ, Kertesz S, Davies S, Turan JM. Using Patient Perspectives to Inform the Development of a Behavioral Intervention for Chronic Pain in Patients with HIV: A Qualitative Study. Pain Med. 2017 May 1;18(5):879-888. PubMed PMID: 27425186.
2. Merlin JS, Bulls HW, Vucovich LA, Edelman EJ, Starrels JL. Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. AIDS Care. 2016 Dec;28(12):1506-1515. PubMed PMID: 27267445; PubMed Central PMCID: PMC5053858.
3. Merlin JS, Tamhane A, Starrels JL, Kertesz S, Saag M, Cropsey K. Factors Associated with Prescription of Opioids and Co-prescription of Sedating Medications in Individuals with HIV. AIDS Behav. 2016 Mar;20(3):687-98. PubMed PMID: 26487298; PubMed Central PMCID: PMC4777647.
4. Merlin JS, Walcott M, Kerns R, Bair MJ, Burgio KL, Turan JM. Pain self-management in HIV-infected individuals with chronic pain: a qualitative study. Pain Med. 2015 Apr;16(4):706-14. PubMed PMID: 25645646; PubMed Central PMCID: PMC4390451.

B. Positions and Honors

Positions and Employment

2011 - 2017	Assistant Professor, University of Alabama at Birmingham, Birmingham, AL
2017 -	Visiting Associate Professor, University of Pittsburgh School , Pittsburgh, PA

Other Experience and Professional Memberships

2010 -	HIV and pain guidelines panel, Infectious Diseases Society of America
2010 - 2013	Founding Chair, HIV Special Interest Group, American Academy of Hospice and Palliative Medicine
2014 -	Various committees (abstract, travel awards), Association for Medical Education and Research in Substance Abuse
2014 -	Founding Co-Chair, Primary Care Shared Interest Group, American Pain Society

Honors

2010	Penn Pearls Teaching Award, University of Pennsylvania
2011	Young Investigator Award, American Academy of Hospice and Palliative Medicine
2014	Hospice and Palliative Medicine Inspirational Leader Under 40, American Academy of Hospice and Palliative Medicine
2018	John C. Liebeskind Early Career Scholar Award, American Pain Society

C. Contribution to Science

1. Growing Awareness of Chronic Pain as an Important Comorbidity in Individuals with HIV: As an infectious diseases fellow, I was one of the first investigators to formally describe the high prevalence of chronic pain in individuals with HIV (39-85% in currently published studies). This early work suggested that among individuals with HIV, those with psychiatric illness are 40% more likely to have chronic pain, and those with intravenous drug use are more likely to have moderate or severe pain than patients without intravenous drug use. Using a large cohort of individuals with HIV in the Southeastern US, I led one of the first studies to investigate the relationship between chronic pain and key HIV outcomes. This study showed that individuals with HIV who had chronic pain had up to 10 times greater odds of functional impairment than individuals who had HIV who did not have chronic pain. Additionally, it showed that individuals with HIV who have chronic pain and also report current substance use are more likely to attend HIV primary care visits than individuals with HIV who have chronic pain but do not report current substance use. This suggests a complex relationship between chronic pain, substance use, and retention in HIV primary care

that will be an important consideration in interventions such as the one proposed in this study targeted to improve chronic pain in this population.

a. Merlin JS, Westfall AO, Chamot E, Overton ET, Willig JH, Ritchie C, Saag MS, Mugavero MJ. Pain is independently associated with impaired physical function in HIV-infected patients. Pain Med. 2013 Dec;14(12):1985-93. PubMed PMID: 24119077; PubMed Central PMCID: PMC3886835.
b. Merlin JS, Westfall AO, Raper JL, Zinski A, Norton WE, Willig JH, Gross R, Ritchie CS, Saag MS, Mugavero MJ. Pain, mood, and substance abuse in HIV: implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. J Acquir Immune Defic Syndr. 2012 Oct 1;61(2):164-70. PubMed PMID: 22766967; PubMed Central PMCID: PMC3459261.
c. Merlin JS, Cen L, Praestgaard A, Turner M, Obando A, Alpert C, Woolston S, Casarett D, Kostman J, Gross R, Frank I. Pain and physical and psychological symptoms in ambulatory HIV patients in the current treatment era. J Pain Symptom Manage. 2012 Mar;43(3):638-45. PubMed PMID: 22115794; PubMed Central PMCID: PMC3786171.

2. Psychosocial aspects of chronic pain in HIV: I led the development of the first biopsychosocial framework for chronic pain adapted to individuals with HIV. This framework was the basis for a qualitative study of the chronic pain experience in patients with HIV. This qualitative work highlighted HIV-infected patients' perceptions of the importance of comorbid mood disorders and substance use in their chronic pain. Additionally, as part of this study, patients described a high degree of pain self-management without ever having received formal instruction. These results have formed the basis of the behavioral intervention I developed and piloted during my K23, and which will be tested in a full-scale efficacy trial in the present proposal.

a. Merlin JS, Walcott M, Kerns R, Bair MJ, Burgio KL, Turan JM. Pain self-management in HIV-infected individuals with chronic pain: a qualitative study. Pain Med. 2015 Apr;16(4):706-14. PubMed PMID: 25645646; PubMed Central PMCID: PMC4390451.
b. Merlin JS, Zinski A, Norton WE, Ritchie CS, Saag MS, Mugavero MJ, Treisman G, Hooten WM. A conceptual framework for understanding chronic pain in patients with HIV. Pain Pract. 2014 Mar;14(3):207-16. PubMed PMID: 23551857.
c. Merlin JS, Walcott M, Ritchie C, Herbey I, Kertesz SG, Chamot E, Saag M, Turan JM. 'Two pains together': patient perspectives on psychological aspects of chronic pain while living with HIV. PLoS One. 2014;9(11):e111765. PubMed PMID: 25365306; PubMed Central PMCID: PMC4218809.

3. Development of a behavioral intervention for chronic pain in individuals with HIV: As part of my K23 career development award, I have used qualitative investigations of patient preferences and the rigorous process of intervention mapping to systematically develop a behavioral intervention for chronic pain tailored to individuals with HIV. Our systematic review of the literature found only 2 published behavioral interventions, both with significant limitations, providing a rationale for this work. Initial qualitative work suggested that the intervention should have a one-on-one skill-building component with an expert interventionist, a group component to build community around HIV and pain and share strategies for success, and a peer component to provide guidance on how to manage chronic pain and living with HIV.

a. Merlin JS, Young SR, Johnson MO, Saag M, Demonte W, Modi R, Shurbaji S, Anderson WA, Kerns R, Bair MJ, Kertesz S, Davies S, Turan JM. Using patient perspectives to inform the development of a behavioral intervention for chronic pain in patients with HIV: a qualitative study. Pain medicine (Malden, Mass.). Forthcoming;
b. Merlin JS, Bulls HW, Vucovich LA, Edelman EJ, Starrels JL. Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. AIDS Care. 2016 Dec;28(12):1506-1515. PubMed PMID: 27267445; PubMed Central PMCID: PMC5053858.

4. Concerning behaviors that arise among individuals prescribed long-term opioid therapy, including using more medications than prescribed and obtaining prescriptions from multiple providers, are common in patients on long-term opioid therapy. However, there is no evidence to guide their management. We conducted a national, four-round Delphi study to develop consensus among expert pain and opioid

clinicians on the management of the six most common and challenging behaviors identified by our participants.

a. Merlin JS, Young SR, Starrels JL, Azari S, Edelman EJ, Pomeranz J, Roy P, Saini S, Becker WC, Liebschutz JM. Managing Concerning Behaviors in Patients Prescribed Opioids for Chronic Pain: A Delphi Study. J Gen Intern Med. 2018 Feb;33(2):166-176. PubMed PMID: 29204977; PubMed Central PMCID: PMC5789105.
b. Merlin JS, Young SR, Azari S, Becker WC, Liebschutz JM, Pomeranz J, Roy P, Saini S, Starrels JL, Edelman EJ. Management of problematic behaviours among individuals on long-term opioid therapy: protocol for a Delphi study. BMJ Open. 2016 May 6;6(5):e011619. PubMed PMID: 27154486; PubMed Central PMCID: PMC4861114.
c. Becker WC, Merlin JS, Manhapra A, Edens EL. Management of patients with issues related to opioid safety, efficacy and/or misuse: a case series from an integrated, interdisciplinary clinic. Addict Sci Clin Pract. 2016 Jan 28;11(1):3. PubMed PMID: 26818474; PubMed Central PMCID: PMC4730605.

5. Understanding the pathophysiology of chronic pain in the current antiretroviral (ART) treatment era: Chronic pain is especially common in PLWH. However, reasons for this are unclear. I lead two lines of research on this topic. 1) Inflammation as a putative mechanism for chronic pain in PLWH: Our findings show that that IL-1β levels are associated with chronic multisite pain in PLWH. 2) Pain sensitivity: PLWH are more pain sensitive than individuals who are HIV negative, and also, PLWH with detectable viral loads are more pain sensitive than PLWH with undetectable viral loads.

a. Merlin JS, Westfall AO, Heath SL, Goodin BR, Stewart JC, Sorge RE, Younger J. Brief Report: IL-1β Levels Are Associated With Chronic Multisite Pain in People Living With HIV. J Acquir Immune Defic Syndr. 2017 Aug 1;75(4):e99-e103. PubMed PMID: 28328552; PubMed Central PMCID: PMC5484722.
b. Goodin BR, Owens MA, Yessick LR, Rainey RL, Okunbor JI, White DM, Mushatt KA, Harmon OA, Heath SL, Merlin JS. Detectable Viral Load May Be Associated with Increased Pain Sensitivity in Persons Living with HIV: Preliminary Findings. Pain Med. 2017 Dec 1;18(12):2289-2295. PubMed PMID: 28398572.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/jessica.merlin.1/bibliography/44127485/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

K23 MH104073-01A1
Merlin, Jessica S (PI)
12/15/14-11/30/18
Development of a Behavioral Intervention for Chronic Pain in Individuals with HIV
The goal of this proposal is to use intervention mapping involving detailed qualitative investigations to develop and pilot test a behavioral intervention for chronic pain in individuals with
Role: PI

Completed Research Support

K12 HS021694-02
Saag, Kenneth G (PI)
08/01/12-12/31/14
UAB K12 in Patient Centered Outcomes Research
Screening for and Understanding Chronic Pain in HIV-infected patients: The goal of this career development award is to support Dr. Jessica Merlin in Patient-Centered Outcomes Research and Career Development in

HIV and chronic pain. The focus of this project is to adapt, pilot test, and validate a Brief Chronic Pain Screening tool in HIV-infected patients, and learn more about the chronic pain experience in this population.
Role: TA

Palliative Research Enhancement Project, University of Alabama at Birmingham
Merlin, Jessica S (PI)
10/01/14-09/30/15
Development of a Behavioral Intervention for Chronic Pain in Individuals with HIV
The goal of this grant is to provide funding to allow Dr. Merlin to conduct the qualitative work necessary to develop a behavioral intervention for chronic pain in individuals with HIV.
Role: PI

UL1 TR00165-05, National Institutes of Health
Kimberly, Robert (PI)
05/01/12-04/30/13
The Role of Chronic Pain and Age in HIV Outcomes
The goal of this pilot study is to evaluate the association between chronic pain and age, alone and in the context of psychiatric illness and substance abuse, on health behaviors and clinical outcomes in patients with HIV.
Role: TA

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Burel		Goodin		PD/PI		4.8					
2 .		Justin		Thomas		Co-Investigator		3.6					
3 .		Jarred		Younger		Co-Investigator		1.2					
4 .		Dusint		Long		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
2	Graduate Students	6.0				0.00	
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Manager	12.0					
3	**Total Number Other Personnel**						

Total Other Personnel

Total Salary, Wages and Fringe Benefits (A+B)

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	54,000.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	46,066.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Participant incentives	12,000.00
9 . CRU/Blood Collection/Assays/CD4/CD8	68,034.00
10 . Tuition Remission	32,000.00
Total Other Direct Costs	**212,100.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**467,547.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	48.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**668,570.00**

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	668,570.00

L. Budget Justification*	File Name: R01_Budget_Justification_4.23.18.EKW.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Burel		Goodin		PD/PI		4.8					
2 .		Justin		Thomas		Co-Investigator		3.6					
3 .		Jarred		Younger		Co-Investigator		1.2					
4 .		Dusint		Long		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
2	Graduate Students	6.0				0.00	
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Manager	12.0					
3	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	31,750.00
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	47,072.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Participant incentives	24,000.00
9 . CRU/Blood Collection/Assays/CD4/CD8	72,084.00
10 . Tuition Remission	32,000.00
Total Other Direct Costs	**206,906.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	48.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification* File Name: R01_Budget_Justification_4.23.18.EKW.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Burel		Goodin		PD/PI		4.8					
2 .		Justin		Thomas		Co-Investigator		3.6					
3 .		Jarred		Younger		Co-Investigator		1.2					
4 .		Dusint		Long		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
2	Graduate Students	6.0				0.00	
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Manager	12.0					
3	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	31,750.00
2. Publication Costs	2,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	48,110.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Participant incentives	24,000.00
9 . CRU/Blood Collection/Assays/CD4/CD8	72,489.00
10 . Tuition Remission	32,000.00
Total Other Direct Costs	**210,349.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	48.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification* File Name: R01_Budget_Justification_4.23.18.EKW.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Burel		Goodin		PD/PI		4.8					
2 .		Justin		Thomas		Co-Investigator		3.6					
3 .		Jarred		Younger		Co-Investigator		1.2					
4 .		Dusint		Long		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
2	Graduate Students	6.0				0.00	
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Manager	12.0					
3	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	31,750.00
2. Publication Costs	2,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	49,177.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Participant incentives	24,000.00
9 . CRU/Blood Collection/Assays/CD4/CD8	72,489.00
10 . Tuition Remission	32,000.00
Total Other Direct Costs	**211,416.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	48.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification* File Name: R01_Budget_Justification_4.23.18.EKW.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Burel		Goodin		PD/PI		4.8					
2 .		Justin		Thomas		Co-Investigator		3.6					
3 .		Jarred		Younger		Co-Investigator		1.2					
4 .		Dusint		Long		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
2	Graduate Students	6.0				0.00	
	Undergraduate Students						
	Secretarial/Clerical						
1	Project Manager	12.0					
3	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0636907050000
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	31,750.00
2. Publication Costs	2,000.00
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	49,759.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Participant incentives	12,000.00
9 . CRU/Blood Collection/Assays/CD4/CD8	68,237.00
10 . Tuition Remission	32,000.00
Total Other Direct Costs	**195,746.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	48.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS Shon Turner 214-767-3261

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification* File Name: R01_Budget_Justification_4.23.18.EKW.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

Budget Justification

Below, we explain the specific roles and justification for all personnel and other requested budget items. These requested expenditures are justified by the nature of the proposed research. Specifically, we propose to investigate the impact of insomnia on pain, physical function, and inflammation in people living with HIV. Across the study timeline, we will collect an extensive array of data in order to address our mechanistic hypotheses, including objective (actigraphy) and subjective (daily diaries) sleep data, experimental pain sensitivity testing, physical performance on a functional battery, and inflammatory biomarker assays. Given the expertise and personnel effort required to complete the proposed studies, we believe the requested budget is fully justified.

A. Senior/Key Personnel

Burel R. Goodin, Ph.D., Principal Investigator, (4.8 Calendar Months, 40% FTE years 1-5). Dr. Goodin has conducted multiple studies examining individual differences in pain sensitivity using the experimental pain testing equipment and protocols presented in this proposal. In addition to serving as PI for 2 of the 3 previously conducted pilot studies presented in this proposal, Dr. Goodin's previous and ongoing research has investigated the effects of discrimination and stigma on clinical pain outcomes, experimental pain sensitivity, and immune system responses among racial minority groups with HIV. Responsibilities for the current proposal will include coordination of all aspects of the proposed study, including experimental design, data acquisition, data management and analysis, interpretation of results, and scientific presentation of findings. Additionally, Dr. Goodin will oversee participant recruitment from the 1917 HIV clinic, scheduling, and participant management by the Clinical Research Unit coordinator and the research assistants.

Stephen Justin Thomas, Ph.D., Co-investigator, (3.6 Calendar Months, 30% FTE years 1-5). Dr. Thomas is an Assistant Professor in the Department of Psychiatry and Behavioral Neurobiology at the University of Alabama at Birmingham. Dr. Thomas has expertise in behavioral sleep medicine, and has considerable experience conducting research addressing the impact of sleep disorders on health outcomes including pain, hypertension, and inflammation in healthy volunteers and clinical samples. Clinically, Dr. Thomas is the Director of the Behavioral Sleep Medicine Clinic and Training Program in affiliation with the UAB Sleep/Wake Disorders Center. He will serve as the insomnia and sleep expert for the purpose of this proposal. Among others, Dr. Thomas's responsibilities for the current proposal will include overseeing the administration of the Diagnostic Interviews for Sleep Patterns and Disorders (DISP), and interpretation of sleep data for the accurate classification of PLWH with insomnia and without. He will also coordinate the organization, management, and interpretation of actigraphy data in order to accurately quantify insomnia burden. He has significant experience in cleaning and interpreting actigraphy data for research purposes, as well as clinically in the UAB Sleep/Wake Disorders Center. He will be integrally involved with manuscript preparation and publication.

Jessica S. Merlin, M.D., Co-investigator, (1.2 Calendar Months, 10% FTE years 1-5). Dr. Merlin is an Associate Professor of Medicine at the University of Pittsburgh and a practicing HIV physician. Despite now being located in Pittsburgh, she remains actively engaged in research projects at UAB, and she is extremely familiar with the UAB 1917 HIV clinic, its patients, and how it operates. Dr. Merlin has an extensive track-record of research involvement and productivity. She has developed expertise in HIV and chronic pain over the past 10 years, beginning with her infectious diseases and palliative care fellowships. She is currently one of only three people in the US fellowship trained in both of these disciplines. Dr. Merlin has known Dr. Goodin for approximately 6 years, and they have already collaborated on three pilot studies, with plans to collaborate on many more in the future. They are also establishing a publication record together given several recently published manuscripts on which they were co-authors. Responsibilities for this application will include assisting the PI on all aspects of the project, with specific emphasis on assisting with recruitment, the medical evaluation of participants via electronic medical records, assessment of health history and medical comorbidities. This will all be done to determine appropriateness of patients for continued matriculation through the study protocols. She will also assist our coordination with CRU study staff to facilitate study protocols and data collections, and assist with interpretation of study results and preparation of findings for publication.

Jarred Younger, Ph.D., Co-investigator, (1.2 Calendar Months, 10% FTE years 1-5). Dr. Younger is an Associate Professor in the UAB Department of Psychology and a well-established pain and fatigue researcher, with expertise in the neuroinflammatory mediators of poor pain and fatigue outcomes. Approximately, 3 years

ago Dr. Younger relocated to UAB from Stanford University. Since that time, Dr. Younger has established, and continues to grow, a collaborative relationship with Dr. Goodin. Dr. Goodin has served as a co-investigator for Dr. Younger's most recent R01 award addressing daily immune markers of pain and fatigue symptoms in patients with chronic fatigue syndrome. Dr. Younger's responsibilities for the current proposal will include assisting the PI on all aspects of the project, with specific emphasis on guiding the processes and protocols for satisfactory blood collection, processing and storage, as well as assay for quantification of inflammatory biomarkers. He will also assist specifically with interpretation of inflammatory biomarker data, and more broadly with interpretation of study results. He will also be available to coordinate appropriate assay specifications with Dr. Barbara Gower, who will complete all assays in her laboratory (see letter of support from Dr. Gower).

Dustin M. Long, Ph.D., Co-Investigator and Biostatistician, (1.2 Calendar Months, 10% FTE years 1-5). Dr. Long was recently recruited to UAB, and he is currently as Assistant Professor of Biostatistics in the School of Public Health. He has an established track-record of involvement in projects focused on persons living with HIV/AIDS. During his training at the University of North Carolina at Chapel Hill, he assisted several HIV investigators in the UNC CFAR as a graduate assistant under Dr. Michael Hudgens. Additionally, Dr. Long's dissertation developed several biostatistical methods pertaining to HIV studies. Since coming to UAB, he has begun with the UAB CFAR as a biostatistician, providing biostatistical support to all CFAR members or to those researching diseases and behaviors related to HIV. Dr. Long is well-versed in multivariate statistical methods, including the analysis of complex interactions among biological and behavioral variables. Dr. Long will oversee all aspects of data analysis, and he will provide invaluable assistance with effective data management practices. Dr. Long has been instrumental in developing the analytic plan for the proposed project, which he will carry out when the data are collected.

B. Other Personnel

Project Manager TBN: (12.0 calendar months, 100% FTE years 1-5). For the proposed study, the project manager will coordinate and manage all project-related activities; interface with study participants; supervise assessments; manage blood draws in CRU; disseminate study findings to the community; prepare weekly team meetings to monitor project goals; assist in preparing annual reports to IRB and NIH.

Graduate Students TBN: (6.0 calendar months, 50% FTE years 1-5). Funds are requested to support two graduate students as part of this study. Duties will include assisting the PI and co-investigators in all aspects of subject recruitment and scheduling as well as data collection and data management. The graduate students will also assist with the collection of sleep data, conduct of experimental pain testing sessions, as well as processing samples for biomarker assays. The graduate students will be necessary for performing data collection and ensuring participant retention.

C. Fringe Benefits

The fringe benefit rates of 29.4% for faculty, 35.3% for project managers, and 0% for graduate students are based on the proposed Federally Negotiated Rate Agreement for FY 18/19.

D. Equipment Description

None.

E. Travel

$5,000 is requested per year to cover expenses for the PI and graduate students to travel and present data at a national meeting such as the Conference on Retroviruses and Opportunistic Infections (CROI), the American Pain Society (APS), or the National Sleep Conference (SLEEP). This budget will cover airfare, lodging and meal expenses for up to three days per meeting attended.

F. Participant/Trainee Support Costs

N/A

G. Other Direct Costs

Actigraphy: $6,000 is requested per year to purchase actigraphs. Objective sleep data will be acquired using the Actiwatch2 (Respironics, Bend, OR), a wrist-worn, watch-like actigraph. The Actiwatch2 is priced at $600 per unit, and this budget cost will allow us to purchase 10 actigraphs. This will be a recurring cost each year in order to replace broken and/or lost actigraphs. Multiple actigraphs will help ensure that participant matriculation through the study is not slowed due to lack of units available for use.

Actigraphy Software: $1,500 is requested in only Year 1 of the project to cover the purchase of necessary software that allows the actigraphy units to be configured, as well as management and configuration of sleep data. This money will also be used to purchase several charging stations needed to charge the battery for each actiwatch.

Laptop: $2,000 is budgeted in Year 1 to cover the cost of a laptop computer that will only be used to run and support the software required for managing the actigraphic sleep data.

Home Sleep Monitoring: The Resmed ApneaLink Air device (Resmed, San Diego, CA) can be leased from the ResMed company for $600 per year. Funds are requested to lease four devices per year across the five-year duration of the project. Furthermore, there are consumables that must be purchased (e.g., sensors, belt, adhesive strips) each year for approximately $600. Altogether, we request that $3,000 per year be allocated to the costs of home sleep monitoring.

Laboratory Materials & Supplies: $5,000 is requested per year to cover the costs of study-related computer, research and laboratory supplies. This includes removable media for storing and backing up data files (e.g. CD-ROMs, flash drives, etc…). In addition, budget is requested to purchase patient charts for archiving hardcopies of recorded data. Other laboratory supplies including stop watches for experimental pain testing as well as freezer racks, pipets, and gloves for blood processing will be required.

Equipment Maintenance and Customer Support: $2,000 is requested each year to cover the costs of repairs and customer service that is often required for the experimental pain testing equipment. For instance, the manufacturer's warranty for the Thermal Sensory Analyzer –II currently in Dr. Goodin's possession has expired. Any repair/service costs moving forward will be billed directly to Dr. Goodin. Therefore, a recurring budget for equipment maintenance and customer support is requested for each year to assist with keeping all of the study equipment functional and in good working order.

Publication Costs: In Years 3, 4, and 5, $2,000 has been requested for each year to cover the cost of publication in open access journals. Publication in open access journals is important because it allows all both scientific and lay readers the opportunity to access scholarly information without financial, legal, or technical barriers. While open access journals are freely available to the reader, there are still costs associated with the publication and production of such journals.

Tuition Remission: It is anticipated that the graduate students recruited to help coordinate and facilitate the proposed study will be UAB doctoral students in the Department of Psychology. In addition to salary support, $32,000 is being requested per year ($16,000 per student) to cover the costs of the student's tuition (i.e., tuition remission). Given graduate student's integral and important role in the study, we feel this budget expenditure to be justified.

H. Per Participant Costs

Below we summarize the expected participant flow and the per participant costs for biomarker assays, facility fees, and participant payment over the 5-year budget period. We will over-enroll by 20% to accommodate for participant attrition and incomplete study participation. Therefore, the proposed budget will cover costs associated with enrolling a total of 240 people (60 PLWH with insomnia, 60 PLWH without insomnia, 60 non-HIV with insomnia, 60 non-HIV without insomnia) for Specific Aim 1, with 120 participants (60 PLWH with insomnia, 60 non-HIV with insomnia) carried forward for Specific Aim 2.

Participant Payment: For Specific Aim 1, participant payment is budgeted at $100 for each of the two study sessions. Additionally, participants will be compensated $50 for successfully wearing the actiwatch and completing sleep diaries for the 7 days/nights between the two study sessions. Funds are being requested for the anticipated recruitment of 240 total participants for Specific Aim 1. For Specific Aim 2, $50 will be paid for each of the six study visits completed by the anticipated 120 participants with insomnia. All participants in this study will receive $250 for completing Specific Aim 1. The 120 with insomnia (60 PLWH, 60 non-HIV) identified in Aim 2 will receive an additional $300 for completing Specific Aim 2. This amount of payment per participant is comparable to previous participant remuneration for studies of similar time commitment and invasiveness at our institution.

Clinical Research Unit: All sessions will be conducted in the UAB Clinical Research Unit (CRU), which is a resource provided to investigators by the Center for Clinical and Translational Science (CCTS). The CRU is a core facility that charges facility fees in order to support the infrastructure. These fees cover the costs of operating and maintaining the CRU rooms, the costs of nursing services, technical support, and scheduling. The discounted facility fee is $15 per participant per visit to the CRU. There will be 2 visits to the CRU for Specific Aim 1 and an additional 6 visit to the CRU for Specific Aim 2. Years 3, 4, and 5 are adjusted for anticipated 5% cost inflation.

Blood Collection & Processing: Blood will initially be collected and processed in the CRU by the specimen processing staff. Processed blood will be stored at the UAB Biorepository until it can subsequently be transferred to the laboratory of Dr. Barbara Gower for immunoassay. During the second experimental sessions included in Specific Aim 1, a CRU nurse will place an IV catheter and collect 5 blood samples so inflammatory reactivity can be examined. These 5 samples will be processed and aliquoted in duplicate (10 aliquots per participant) prior to being stored in a -80^{o}C freezer. For Specific Aim 2, each week following collection of sleep data, participants will have blood drawn using a butterfly needle. The cost of collecting and processing the blood is $15 per participant per visit to the CRU. Blood will be collected as part of a single session for 240 participants (Aim 1), and 6 collections of blood across 6 sessions for 120 participants as part of Aim 2. Years 3, 4, and 5 are adjusted for an anticipated 5% cost inflation.

Cytokine Assays: TNF-α, IL1-β, IL-4, IL-6, IL-10, IL-12, IL-13, IL-18, IFN-gamma, IFN-alpha, and TGF-beta will be assayed at UAB by Dr. Barbara Gower within the Physiology and Metabolism Core. These cytokines will be collected and analyzed as part of Specific Aim 1. The cost for assaying each of these cytokines is approximately $7.00 apiece. There are 11 cytokines and each will be sampled 5x per participant (240 participants) for Aim 1, as well as 6x per participant (120 participants) for Aim 2. The requested budget for these cytokines covers the cost of purchasing kits and reagents, sample preparation, and labor costs for performing assays, including quality control steps.

Other Inflammatory Assays: High sensitivity C-reactive protein, sCD14/163, and D-dimer will also be assayed by Dr. Barbara Gower in order to fulfill Aims 1 and 2. The costs for assaying each of these inflammatory markers is $15 per analyte. Budget is requested to cover costs associated with collecting these four markers as part of Aims 1 and 2. Again, the requested budget for these biomarkers covers the cost of purchasing kits and reagents, sample preparation, and labor costs for performing assays, including quality control steps.

CD4/CD8 and viral load: CD4/CD8 (their ratio), nadir CD4, and viral load counts will be determined in real time for all study participants. This will occur as part of the second session for Specific Aim 1. For the 120 PLWH with and without insomnia, this will allow for greater appreciation of HIV-related health, while for 120 non-HIV participants with and without insomnia, this will confirm their HIV status. The cost for quantifying CD4/CD8 and viral load for each participant is $237.

I. Data Management

REDCap and DOT-IT: An annual budget of $12,000 is requested to cover the costs of maintaining and updating the secure web-based data management system (i.e., REDCap). In addition to this annual fee, DOT-IT also charges $75/hour for assistance with building a study-specific database. The budget for this service is much more heavily weighted at the beginning of the study period, when the most time and effort will be invested in

building the study database ($22,500; $75/hour x 300 hours). In the years following the first, the cost of managing and supporting the REDCap database is budgeted at much less ($3,750; $75/hour x 50 hours). The REDCap system will be used by study participants to complete questionnaires, which will avoid the costs associated with developing and maintaining paper forms, and prevents errors and costs associated with transferring data collected on paper into computer databases. The REDCap system will also be able to generate enrollment reports, adverse event tables, and to score questionnaires on request. In addition to building the REDCap data management system for this study, the requested costs will cover ongoing technical support, report creation, and database management and oversight.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		
Section B, Other Personnel		
Total Number Other Personnel	15	
Total Salary, Wages and Fringe Benefits (A+B)		
Section C, Equipment		0.00
Section D, Travel		25,000.00
1. Domestic	25,000.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		
1. Materials and Supplies	181,000.00	
2. Publication Costs	6,000.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	240,184.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	96,000.00	
9. Other 2	353,333.00	
10. Other 3	160,000.00	
Section G, Direct Costs (A thru F)		
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		
Section J, Fee		0.00
Section K, Total Costs and Fee (I + J)		3,363,347.00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Pittsburg

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jessica		Merlin		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: University of Pittsburg

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2018 **End Date*:** 08-31-2019 **Budget Period: 1**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**0.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Modified Total Direct Costs	56.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS Steven Zuraf 301-492-4855

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Total Costs and Fee	**Funds Requested ($)***

L. Budget Justification* File Name: UPitt_Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Pittsburg

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jessica		Merlin		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**

Total Salary, Wages and Fringe Benefits (A+B)

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Organization: University of Pittsburg

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2019 **End Date*:** 08-31-2020 **Budget Period: 2**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**0.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Modified Total Direct Costs	56.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS Steven Zuraf 301-492-4855

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Total Costs and Fee	**Funds Requested ($)***

L. Budget Justification* File Name: UPitt_Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Pittsburg

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jessica		Merlin		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2020 **End Date*:** 08-31-2021 **Budget Period: 3**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**0.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Modified Total Direct Costs	56.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number): DHHS Steven Zuraf 301-492-4855

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Total Costs and Fee	**Funds Requested ($)***

L. Budget Justification* File Name: UPitt_Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Pittsburg

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jessica		Merlin		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**

Total Salary, Wages and Fringe Benefits (A+B)

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2021 **End Date*:** 08-31-2022 **Budget Period: 4**

F. Other Direct Costs	**Funds Requested ($)***
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**0.00**

G. Direct Costs	**Funds Requested ($)***
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	**Funds Requested ($)***
1 . Modified Total Direct Costs	56.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS Steven Zuraf 301-492-4855

I. Total Direct and Indirect Costs	**Funds Requested ($)***
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	**Funds Requested ($)***

K. Total Costs and Fee	**Funds Requested ($)***

L. Budget Justification* File Name: UPitt_Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: 0045143600000

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: University of Pittsburg

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Jessica		Merlin		Co-Investigator		1.2					

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: **Total Senior/Key Person**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	**0.00**
						Total Salary, Wages and Fringe Benefits (A+B)	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
Equipment Item		**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file		
	Total Equipment	**0.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	
Total Travel Cost	**8,000.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other:		
Number of Participants/Trainees	**Total Participant Trainee Support Costs**	**0.00**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: 0045143600000
Budget Type*: ❍ Project ● Subaward/Consortium
Organization: University of Pittsburg

Start Date*: 09-01-2022 **End Date*:** 08-31-2023 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
Total Other Direct Costs	**0.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . Modified Total Direct Costs	56.5		
		Total Indirect Costs	

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS Steven Zuraf 301-492-4855

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*

L. Budget Justification* File Name: UPitt_Budget_Justification.pdf
(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

University of Pittsburg Budget Justification

Jessica S. Merlin, M.D., Co-investigator, (1.2 Calendar Months, 10% FTE years 1-5). Dr. Merlin is an Associate Professor of Medicine at the University of Pittsburgh and a practicing HIV physician. Despite now being located in Pittsburgh, she remains actively engaged in research projects at UAB, and she is extremely familiar with the UAB 1917 HIV clinic, its patients, and how it operates. Dr. Merlin has an extensive track-record of research involvement and productivity. She has developed expertise in HIV and chronic pain over the past 10 years, beginning with her infectious diseases and palliative care fellowships. She is currently one of only three people in the US fellowship trained in both of these disciplines. Dr. Merlin has known Dr. Goodin for approximately 6 years, and they have already collaborated on three pilot studies, with plans to collaborate on many more in the future. They are also establishing a publication record together given several recently published manuscripts on which they were co-authors. Responsibilities for this application will include assisting the PI on all aspects of the project, with specific emphasis on assisting with recruitment, the medical evaluation of participants via electronic medical records, assessment of health history and medical comorbidities. This will all be done to determine appropriateness of patients for continued matriculation through the study protocols. She will also assist our coordination with CRU study staff to facilitate study protocols and data collections, and assist with interpretation of study results and preparation of findings for publication.

Fringe Benefits:

Fringe benefits are calculated at the University of Pittsburgh's pending DHHS rates of 25.5% for medical faculty.

Travel

$8,000 is budgeted per year to cover the costs associated with Dr. Merlin traveling from Pittsburgh to Birmingham quarterly (4x per year) to assist with the study at UAB campus. This budget will cover the costs of airfare, lodging, and meal expenses for three days per visit."

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		
Section B, Other Personnel		0.00
Total Number Other Personnel	0	
Total Salary, Wages and Fringe Benefits (A+B)		
Section C, Equipment		0.00
Section D, Travel		40,000.00
1. Domestic	40,000.00	
2. Foreign	0.00	
Section E, Participant/Trainee Support Costs		0.00
1. Tuition/Fees/Health Insurance	0.00	
2. Stipends	0.00	
3. Travel	0.00	
4. Subsistence	0.00	
5. Other	0.00	
6. Number of Participants/Trainees	0	
Section F, Other Direct Costs		0.00
1. Materials and Supplies	0.00	
2. Publication Costs	0.00	
3. Consultant Services	0.00	
4. ADP/Computer Services	0.00	
5. Subawards/Consortium/Contractual Costs	0.00	
6. Equipment or Facility Rental/User Fees	0.00	
7. Alterations and Renovations	0.00	
8. Other 1	0.00	
9. Other 2	0.00	
10. Other 3	0.00	
Section G, Direct Costs (A thru F)		
Section H, Indirect Costs		
Section I, Total Direct and Indirect Costs (G + H)		
Section J, Fee		0.00
Section K, Total Costs and Fee (I + J)		

Total Direct Costs less Consortium F&A

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

Category	Budget Period 1	Budget Period 2	Budget Period 3	Budget Period 4	Budget Period 5	TOTALS
Total Direct Costs less Consortium F&A	450,916	452,871	459,925	472,330	464,661	**2,300,703**

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ❍ Yes ❍ No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

❍ Yes ❍ No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

❍ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period *Anticipated Amount ($) *Source(s)

PHS 398 Cover Page Supplement

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ○ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

❑ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ○ Yes ○ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ○ Yes ○ No

5. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	R01_Specific_Aims.pdf
3. Research Strategy*	R01_Research_Strategy.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	Consortium-Contractual-Merlin_SOW.pdf
9. Letters of Support	Letters_of_Support.pdf
10. Resource Sharing Plan(s)	R01_Resource_Sharing_Plan.pdf
11. Authentication of Key Biological and/or Chemical Resources	R01_Authentication.pdf
Appendix	
12. Appendix	

Insomnia is a common and debilitating sleep disorder in persons living with HIV (PLWH), with prevalence estimates ranging from 30-73%, which is higher than in the general adult population (~20%). Insomnia is increasingly viewed as a risk factor for the onset and/or worsening of pain and physical disability. This is particularly relevant for PLWH because estimates of chronic pain development in HIV range from 54-83%. Inflammatory processes represent an important biologic mechanism linking insomnia to pain and poor physical functioning. Insomnia promotes systemic inflammation as well as inflammatory reactivity to physical stressors like pain. There is growing agreement that inflammation can substantially exacerbate pain symptoms in everyday life, as well as increase sensitivity to painful stimuli in the laboratory setting. Furthermore, insomnia burden can vary substantially from week to week, and this variation tends to map on to variations in inflammation, pain severity, and physical functioning over time. Taken together, insomnia may be a significant driver of pain and poor physical functioning in PLWH through the proliferation of inflammatory mediators.

The *overall objective* of this application is to investigate the impact of insomnia on pain, physical functioning, and inflammation in PLWH. Our *central hypothesis* is that insomnia promotes pain symptoms and sensitivity, poor physical functioning, as well as systemic and pain-evoked inflammation in PLWH. This hypothesis is generated from both contemporary literature, and our own preliminary data. In 2017, we conducted a pilot study that examined associations among self-reported insomnia burden, perceived physical disability, inflammation, and pain sensitivity in PLWH using resources provided by the University of Alabama at Birmingham's Center for AIDS Research. We found trends in our data suggesting that insomnia may be associated with enhanced pain sensitivity and greater reactivity of IL-6 and TNF-α to painful stimulation, as well as greater perceived physical disability. We now propose a larger, adequately powered study to confirm these preliminary findings.

Specific Aim 1: To determine whether insomnia promotes increased sensitivity and inflammatory reactivity to pain stimuli in PLWH. This aim will be addressed in the laboratory following completion of structured interviews for sleep disorders, home (ambulatory) sleep monitoring with actigraphy, and validated daily sleep diaries/questionnaires in order to identify PLWH with and without insomnia according to DSM-5 diagnostic criteria. To increase rigor of study design, comparison groups of non-HIV individuals with and without insomnia will also be included. Participants will complete a standardized battery of experimental pain stimuli designed to assess pain sensitivity. Blood will be drawn before, during, and after the painful stimuli to examine pain-evoked inflammatory responses.

Hypothesis 1a: PLWH with insomnia will have significantly increased pain sensitivity (e.g., ↓pain threshold, ↓pain tolerance) compared to PLWH without insomnia and the non-HIV groups with and without insomnia.

Hypothesis 1b: PLWH with insomnia will demonstrate exaggerated pro-inflammatory reactivity and suppressed anti-inflammatory reactivity to the pain stimuli in comparison to PLWH without insomnia as well as the non-HIV groups with and without insomnia; inflammation and pain sensitivity will be correlated

Specific Aim 2: To determine if weekly fluctuations in insomnia burden drive changes in inflammation, pain severity, and physical functioning in PLWH. This aim will be carried out by having the PLWH with insomnia identified in aim 1 and the non-HIV insomnia group wear ambulatory sleep monitoring devices (i.e., actigraphy) and complete daily sleep and pain diaries. Sleep monitoring and daily diaries will be completed for 7 consecutive days, after which blood will be drawn to evaluate inflammatory markers. Participants will then complete a standardized physical function battery. These procedures will be completed at the same time every week over the course of 6 consecutive weeks. Inflammatory markers, pain, and physical functioning following weeks of high insomnia burden will be compared to those following weeks of low insomnia burden.

Hypothesis 2a: Insomnia burden, inflammation, pain severity, and physical function will be significantly worse across the six weeks for PLWH with insomnia compared to the non-HIV with insomnia group.

Hypothesis 2b: Pro-inflammatory markers will be significantly elevated, and pain severity and physical functioning will be significantly worse, following weeks of high insomnia burden in comparison to weeks of low insomnia burden, particularly for PLWH.

Hypothesis 2c: Insomnia-related weekly variability in inflammatory markers will significantly correlate with weekly variability in pain severity and physical functioning.

If our hypotheses are confirmed, we will identify: 1) insomnia as a major driver of pain and physical functioning in PLWH, and 2) inflammation as an important insomnia-related mediator of pain in PLWH. This research could help confirm insomnia as a therapeutic target for the suppression of pain and inflammation in PLWH. This proposal addresses a high/medium priority topic of research (health comorbidity linked to HIV) according to NIH HIV/AIDS Research Priorities and Guidelines for Determining AIDS Funding (NOT-OD-15-137).

RESEARCH STRATEGY

A. Significance

A1. Insomnia is a common sleep disorder. Insomnia is a sleep disorder characterized by difficulty falling asleep, staying asleep, or both, despite adequate opportunity for sleep attainment.[1-3] As a result, people with insomnia may get too little sleep and/or have poor sleep quality. They often do not feel refreshed when they wake up. Current classifications no longer differentiate whether insomnia occurs independently ("primary") or as the result of another mental and/or physical health condition ("comorbid"). Rather, all insomnia diagnoses are now consolidated under a single, chronic insomnia disorder.[4] It has been reported that the one-year point prevalence of insomnia in the U.S. general population is between 10% and 30% of adults.[5-7] When chronic, insomnia is associated with substantial impairments in an individual's quality of life.[8] Insomnia can cause daytime sleepiness and a lack of energy. It also can also promote anxious and depressed mood, as well as irritability.[9,10] It can further complicate physical health maladies such as cardiovascular disease,[11] diabetes mellitus,[12] chronic pain,[13] and suicide.[14]

Criteria for identifying and diagnosing insomnia vary throughout the medical literature. In survey studies, for example, insomnia is frequently identified by a positive response to either question, "Do you experience difficulty sleeping?" or "Do you have difficulty falling or staying asleep?"[1] In studies incorporating sleep monitoring devices, the presence of a long sleep latency, frequent nocturnal awakenings, prolonged periods of wakefulness during the sleep period, and/or even frequent transient arousals are taken as evidence of insomnia.[15] For the purpose of this proposal, insomnia is specified as a disorder with the following diagnostic criteria according to the Diagnostic and Statistical Manual – 5th Edition (DSM-5)[16] and International Classification of Sleep Disorders – 3rd Edition (ICSD-3).[4] (1) Predominant complaint of dissatisfaction with sleep quantity or quality. (2) Difficulty falling asleep, staying asleep, or both. (3) Difficulty with sleep persists despite adequate opportunity and circumstance to sleep. (4) The sleep difficulty is associated with daytime impairment or distress. (5) The sleep difficulty occurs at least 3 times per week and has been a problem for at least 3 consecutive months. *Use of these DSM-5 and ICSD-3 criteria promotes a more rigorous approach to identifying chronic insomnia disorder, referred throughout the remainder of this proposal simply as insomnia.*

A2. Insomnia is an important comorbidity in persons living with HIV (PLWH). Evidence has suggested that PLWH experience a higher prevalence of insomnia than the general population.[17] Whereas the prevalence of insomnia is up to 30% among U.S. adults in any given year, it may be as high as 70% in PLWH.[18,19] There are several factors specifically related to HIV that may help explain the increased prevalence of insomnia in PLWH. There was initial indication early in the HIV epidemic that infection may reduce slow wave sleep (i.e., deep sleep stages),[20-22] but these findings have also been contradicted.[23] It has been suggested that disease exacerbation (based on CD4+ count and viral load) may be associated with poor sleep quality;[24] however, other studies did not support this finding.[25,26] Medications have been implicated in sleep disturbance among PLWH, and the antiretroviral medication most consistently associated with insomnia is the non-nucleoside transcriptase inhibitor efavirenz.[27,28] Lastly, research addressing psychosocial factors related to insomnia in PLWH has suggested that the stress of chronic illness may precipitate acute onset of insomnia, which then becomes a chronic condition that is comorbid to HIV infection.[29] **It is important to note that identifying determinants of insomnia in PLWH is not the focus of this proposal, rather we plan to elucidate the downstream consequences of insomnia specifically as they relate to pain, physical function, and inflammation.**

A3. Pain is a growing concern for PLWH. A recent review of the literature indicated that over half of all PLWH are likely to experience recurring pain symptoms throughout their lifetimes, with increasing prevalence as these individuals age.[30] Peripheral neuropathy resulting from the neurotoxic effects of HIV itself as well as the medications used to treat HIV was widely considered the primary cause of acute and chronic pain early on in the antiretroviral treatment era.[31] However, recent studies suggest a predominance of musculoskeletal pain in PLWH that is non-neuropathic in origin. It is common for chronic pain in PLWH to be widespread, affecting multiple body locations. To illustrate these points, in a large HIV primary care clinic, it was found that the most common types of pain complaints were musculoskeletal in nature.[32] Studies of PLWH seeking treatment for chronic pain have had similar findings. For example, our group found that the most common cause of chronic pain in individuals presenting to an HIV-focused pain clinic was axial back pain.[33] Lastly, it has been reported that the median number of locations of pain in a cohort of PLWH was five.[34] Irrespective of neuropathic or non-neuropathic

etiology, studies of pain clinical epidemiology in PLWH suggest one-year point prevalence estimates between 30% and 85%, which is higher than in the general population (~20%).[30,33,34]

One possible explanation for the greater pain prevalence in PLWH is that HIV infection is associated with increased sensitivity to painful stimuli (i.e., hyperalgesia). Until recently, this possibility had not been directly tested in humans. However, research on this topic is important because heightened pain sensitivity is a risk factor for the development of many different chronic pain conditions.[35-37] In a recent study conducted by our group, 50 PLWH and 50 community-dwelling, healthy adults without HIV (controls) were recruited. Participants completed an experimental pain testing battery to assess various aspects of pain sensitivity including pain threshold detection and pain tolerance in response to noxious pressure and heat stimuli. PLWH demonstrated significantly lower pressure pain thresholds and significantly lower heat pain tolerance compared to controls.[38] *These findings are among the first suggesting that PLWH demonstrate enhanced pain sensitivity, a known risk factor for the development of chronic pain in everyday life.*

A4. Insomnia drives pain and poor physical functioning. 1. Pain: Although derived exclusively from non-HIV infected populations, a more compelling body of research supports our overarching study aim to examine whether insomnia indeed promotes increased pain sensitivity (hyperalgesia), greater experiences of pain in everyday life, and poor physical functioning in PLWH. The prevailing view in the medical and scientific communities has generally been that poor sleep and pain are reciprocally related.[39] Although there is some merit to this viewpoint, it does not accurately capture the current state of the empirical evidence on this topic. In 2013, our group completed a systematic review of the literature in an attempt to update the field on emergent themes pertaining to the directionality and mechanisms of the association of sleep and pain.[40] A key trend emerging from population-based longitudinal studies is that sleep impairments like those characteristic of insomnia reliably predict new incidents and exacerbations of chronic pain.[41-43] Microlongitudinal studies employing deep subjective and objective assessments of sleep and pain support the notion that poor sleep is a stronger, more reliable predictor of pain than pain is of poor sleep.[44-47] Furthermore, it has been posited that insomnia increases pain by exacerbating conditions that cause pain, for instance, by directly sensitizing peripheral nociceptors and/or by affecting central pain inhibitory and pain facilitatory mechanisms, causing a state of generalized hyperalgesia (i.e., increased pain sensitivity).[48-51] 2. Impact on Physical Function: Limited research to date has examined the effects of insomnia on physical function in PLWH, and suggests that insomnia indeed negatively impacts functional capabilities. To illustrate, it was previously shown that sleep latency (a measure of difficulty falling asleep) measured across two weeks of actigraphic sleep monitoring was significantly longer for PLWH compared to controls, and associated with poorer physical functioning and health-related quality of life.[18] Further, PLWH with insomnia were 3.1-fold more likely to have a decline in activities of daily living than those without insomnia.[52]

We are not aware of any research to date specifically designed to examine whether insomnia is a driver of pain in PLWH. However, a limited number of studies have provided initial support for this possibility. For example, in a correlational study of 317 PLWH, Miaskowski and colleagues found that pain was highly prevalent (55%) and associated with immune status (CD4+ T-cell count), race, and **sleep disturbance**, but not with age, gender, or symptoms of fatigue, depression, or anxiety.[53] In another correlational study of 146 adult PLWH conducted by Vosvick and colleagues, greater intensity of pain and stress were associated with greater **sleep disturbance**.[54] On balance, these studies provide tentative support for our hypothesis that insomnia promotes pain symptoms and pain sensitivity in PLWH.

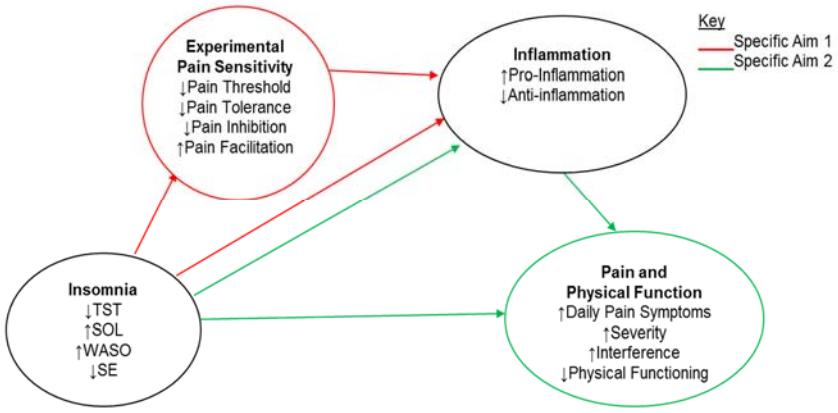
A5. Inflammation is an important biological mechanism linking insomnia with pain and physical function. Mounting evidence from both observational and experimental research suggests that insomnia impacts cytokine levels known to be important in regulating inflammation.[55-57] For example, findings from sleep deprivation studies indicate that sleep loss is associated with increases in pro-inflammatory cytokines (IL-6, TNF-α) as well as acute-phase inflammatory proteins (C-reactive protein).[58] In turn, systemic (peripheral and central) inflammation brought on by chronic insomnia increases the risk of cardiovascular disease, arthritis, and diabetes mellitus.[59,60] We propose that the same inflammatory effects produced by insomnia are also associated with increased experimental pain sensitivity and poor physical function for PLWH. This is because there is currently general agreement that systemic inflammation can substantially exacerbate, if not outright cause, many types of pain[61] and physical disability.[62,63] To illustrate, previous laboratory-based studies have shown that inflammatory markers including IL-6 and C-reactive protein were significantly elevated following a night of sleep restriction (4h versus 8h).[64,65] In turn, these elevated inflammatory markers were strongly associated with increased next-day experimental pain sensitivity in response to sleep restriction [66,67], as well as poor physical function.[65]

HIV envelope glycoproteins such as GP120 and GP160 represent a common biological factor linking insomnia, inflammation, and pain in PLWH. Envelope proteins including GP120 and GP160 are glycoproteins exposed on the cell surface of the HIV envelope. These glycoproteins are responsible for assisting with the fusion of the viral envelope to the cell surface of CD4+ host cells.[68,69] GP120 and GP160 are also responsible for stimulating glial cells in the central nervous system to produce potent cascades of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6.[70-73] GP120 has previously been shown in animal studies to be associated with alterations in sleep consistent with insomnia[74-76] as well as increased pain sensitivity,[77] which were both mediated by inflammation. Whether these findings translate to humans with HIV has yet to be tested; however, HIV envelope proteins represent a plausible link among insomnia, pain, and inflammation. What is currently known is that markers of inflammation are generally higher in PLWH than in the general population, even when they are treated with antiretroviral therapy and achieve virologic suppression.[78,79] Thus, it stands to reason that sleep and pain will be impacted by the elevated inflammation in PLWH.

A6. Summary of significance. Insomnia is an under-appreciated, yet highly prevalent, comorbidity for PLWH with the possibility of far-reaching health consequences. *The overall scientific premise of this proposal is bolstered by past research showing that insomnia is a potent driver of pain and poor physical function, with inflammation as a key biologic mechanism linking insomnia with each.* This is particularly relevant for PLWH given the alarmingly high rate of developing a chronic pain condition as they age. Although yet to be directly tested in PLWH, it stands to reason that inflammation might link insomnia and pain in PLWH given specific characteristics of HIV (i.e., envelope glycoproteins) previously shown in animal studies to underlie all three factors. *This proposal is significant because it is designed to specifically address whether insomnia promotes pain, inflammation, and poor physical functioning in PLWH* (**Figure 1**).

B. INNOVATION

Figure 1: Conceptual model of Insomnia effects on inflammation, pain, and physical function in PLWH



Note: TST = total sleep time, SOL = sleep onset latency, WASO = wake after sleep onset, SE = sleep efficiency

B.1. This proposal is innovative because the impact of insomnia on pain and pain-related inflammatory processes has never before been directly examined in PLWH. We argue that a primary reason for why this proposal is significant also makes it innovative, specifically because this study would be the first to simultaneously address the downstream consequences of insomnia in PLWH as they relate to experiences of pain, physical function, and inflammation. Inflammatory processes associated with insomnia will likely be relevant to many other aspects of health besides pain for PLWH. For this reason, findings generated from this proposal are likely to be of interest to a wide array of medical researchers and healthcare professionals. We chose to specifically focus on pain sensitivity and pain in everyday life in this proposal given the important, albeit deleterious, effects pain can have on quality of life for PLWH.[80] Much like insomnia, pain also appears to be an under-appreciated and under-treated comorbidity for PLWH. *Lastly, we truly appreciate the role depressed and anxious mood can play in insomnia, pain, and even inflammation.[81-85] Although not directly related to the overall aims and hypotheses of this proposal, we plan to measure various aspects of mood (see section D.4. below) throughout the proposed study in order to appropriately characterize the role of psychological functioning in insomnia, pain, and inflammation for PLWH.*

B.2. This proposal is innovative because it will incorporate a combination of objective and subjective sleep assessments to identify insomnia diagnostic criteria and measure insomnia burden. In accordance with consensus guidelines for sleep measurement, both subjective and objective assessments will be considered as the two are only modestly correlated, suggesting that each modality assesses different aspects of an individual's sleep experience.[86,87] *From a technological perspective, the use of actigraphic sleep monitoring in PLWH is innovative given that only a handful of studies, to our knowledge, have used this technology in PLWH over the last 10 years.[88]* These actigraphic studies have generally concluded that sleep disturbance remains problematic in PLWH despite advancements in HIV management.[18,89]

Sleep actigraphs are generally watch-shaped and worn on the wrist of the non-dominant arm. They are useful for determining sleep patterns and disturbances, and may be worn for extended amounts of time.[90-92] Contrary to polysomnography, study participants retain normal levels of mobility and do not need to be located in a laboratory while the required data is being recorded. This permits the study participant to stay in his or her natural sleep environment, which may render the measured data more generally applicable. Actigraphy is being used more actively in sleep-related studies where sleep quality is seen as a good indicator of quality of life. A large reason for this development is the fact that, while retaining mobility, actigraphy offers reliable results with an accuracy that is close to that of polysomnography (above 90%).[93,94] In this study, actigraphic sleep data will be collected across 6 consecutive weeks to measure fluctuations in insomnia burden. "High" burden is conceptualized as shortened total sleep time (≤6 hrs/night), poor sleep efficiency (<85%), and poor self-reported sleep quality. "Low" burden would be >6 hrs/night total sleep, ≥85% sleep efficiency, and good sleep quality.

B.3. This proposal is innovative because it will incorporate objective measures of experimental pain sensitivity and physical functioning in the laboratory setting. The experimental pain testing response measures that will be used in Specific Aim 1 to characterize human pain sensitivity are frequently categorized as either "static" or "dynamic" in nature.[95,96] Traditionally, experimental pain testing has been used in a static way by measuring responses to single discrete stimuli with either fixed intensities or intensities that gradually change over time. More recently, advanced methods of dynamic experimental pain testing were developed whereby stimuli are applied repetitively or simultaneously to different body areas.[97-100] Static measures of pain sensitivity include threshold and tolerance. Two measures of dynamic pain sensitivity include conditioned pain modulation and temporal summation. Greater detail addressing differences between static and dynamic pain sensitivity are provided below in section *D.4.1*. This study will also incorporate objective performance-based measures including the Short Physical Performance Battery and the Timed Up and Go Test (see *E.5* for details). Clinical research suggests that people tend to over over-estimate functional capacity on self-report measures relative to actual performance on objective measures. Therefore, it is important to supplement self-report measures with performance-based measures as both methods provide important and complementary information.

B.4. This proposal is innovative because the association of insomnia with pain-evoked inflammatory reactivity will be examined, in addition to fluctuations in circulating levels of inflammation over time. We propose to examine a wide array of inflammatory markers related to insomnia and pain. In the context of *specific aim 1*, the pro-inflammatory and anti-inflammatory cytokines previously demonstrated as being most associated with insomnia and pain sensitivity will be included. Pro-inflammatory markers will include TNF-α, IL1-β, IL-6, IL-12, IL-18, C-reactive protein, sCD14/163, D-dimer, and IFN-gamma, while anti-inflammatory markers will include IFN-alpha, TGF-beta, IL4, IL-10, and IL-13. An added bonus of including this inflammatory array it that it can help determine whether insomnia alters the inflammatory milieu by promoting pro-inflammation, dampening anti-inflammation, or both following a battery of experimental pain stimuli. As it relates to *specific aim 2*, this proposal will focus on whether fluctuations in inflammation in relation to insomnia burden covary with changes in everyday pain and physical function. *This wide array of inflammatory cytokines and other markers of inflammation will help maximize the likelihood of detecting insomnia-related alterations in inflammation for PLWH.*

B.5. Summary of innovation. *This study is innovative because no other has directly examined the impact of insomnia on inflammation, pain, and physical function in PLWH.* There is good potential that this study will generate novel data that is of interest to other researchers, clinicians, and patients alike. The use of actigraphy for sleep measurement represents a technologically innovative aspect of this study, given that limited research to date has incorporated actigraphy in PLWH. Experimental pain testing, including both static and dynamic pain sensitivity measurements, is potentially important to examine in relation to insomnia among PLWH. This is because heightened pain sensitivity is a risk factor for the development of many different chronic pain conditions. Therefore, it stands to reason that insomnia my drive pain in everyday life for PLWH by promoting enhanced pain sensitivity. Lastly, this study is innovative because it will demonstrate that extent to which inflammation represents a biological mechanism linking insomnia with pain and physical function in PLWH.

C. Approach

C.1. Overview. This grant application proposes the first direct investigation of whether insomnia is a driver of pain, pain-related inflammatory processes, and physical function in PLWH. We will collect HIV health history, demographic, sleep, physical function, pain, clinical, experimental pain testing, inflammatory, and psychosocial data from a total of 240 participants (120 PLWH, 120 non-HIV). Consistent with the currently reported point

prevalence rates of insomnia in PLWH, it is expected that approximately 50-60% of PLWH recruited for this study will meet DSM-5 and ICSD-3 criteria for chronic insomnia disorder, while the remaining 40-50% will not.[17,18] We will also recruit a group of 120 demographically similar non-HIV individuals with and without insomnia to compare to PLWH. Our study design will capture novel, clinically relevant information that may both reflect the progression of insomnia in PLWH and its consequences for important quality of life determinants including pain, physical function, and inflammation. While highly innovative, the proposed study represents a logical extension of the work that has been done by our investigative team. Before providing specific details of the protocol (Sections D.1. through E.4. below), we summarize major findings from several recently completed pilot studies, including preliminary data supporting our proposed aims. The first study **(Study 1; PI: Goodin)** examined differences in experimental pain sensitivity between PLWH and controls without HIV. This initial study helped our team to determine whether PLWH demonstrated any aberrations in their pain sensitivity profiles. The second study **(Study 2; PI: Merlin)** was designed to examine differences in inflammatory biomarkers in PLWH with and without multi-site chronic pain. The purpose of this study was to establish whether the experience of persistent pain was associated with increased inflammation in PLWH. The final study **(Study 3; PI: Goodin)** currently being conducted in our laboratory includes PLWH with and without insomnia according to a clinically validated sleep questionnaire. This study provides tentative evidence that insomnia is a driver of pain, physical function, and inflammation in PLWH, which is consistent with the proposed aims.

C.2. Preliminary Data. For **Study 1**, a total of 50 PLWH were recruited from the UAB 1917 Clinic, a large, urban HIV clinic that provides comprehensive medical, behavioral, and social services to adults with HIV. Fifty community-dwelling, healthy control participants without HIV were also recruited. According to the results presented in **Table 1**, PLWH generally demonstrated increased experimental pain sensitivity compared to controls without HIV. Compared to controls, PLWH had significantly lower static measures of heat pain threshold and tolerance (measured in degrees Celsius). Further, dynamic measures of pain sensitivity also differed between PLWH and controls, such that PLWH demonstrated significantly greater temporal summation of heat pain and significantly less conditioned pain modulation compared to controls. The Cohen's D effect sizes representing the differences in pain sensitivity between PLWH and controls ranged from small to large according to general guidelines - small (0.2), medium (0.5) and large (0.8). A portion of these data were recently published by our group (*Goodin et al. Pain Med. 2017, 18(12), 2289-2295; doi: 10.1093/pm/pnx057*).[38]

Table 1. Pain sensitivity differences between PLWH and controls

Variable	PLWH (n=50)	Controls (n=50)	Sig.	Cohen's D
Heat pain threshold (^{0}C)	43.5 (1.7)	44.6 (1.2)	**.007**	.748
Heat pain tolerance (^{0}C)	47.5 (1.9)	48.7 (2.0)	**.003**	.615
Pressure pain threshold (kPa)	370.8 (234.9)	458.1 (242.7)	.071	.366
Temporal summation – heat 46^{0}C	15.6 (23.8)	4.5 (15.6)	**.009**	.551
Temporal summation – mechanical	6.1 (7.4)	3.8 (6.9)	.109	.321
Conditioned pain modulation	12.6 (34.2)	30.9 (36.9)	**.012**	.514

Note: temporal summation of heat and mechanical pain are presented as delta changes scores, while conditioned pain modulation was calculated as percent change; C = Celsius, kPa = kiloPascals

The second pilot study conducted by our group (**Study 2**) focused on examining differences in inflammatory biomarkers in a sample comprised entirely of 140 PLWH; however, 70 had chronic multi-site pain while the other 70 did not have any pain. The primary hypothesis for this study was that PLWH with chronic multi-site pain would demonstrate significantly elevated inflammatory biomarkers compared to PLWH without pain. Support for this hypothesis would implicate inflammation as a component of the pain phenotype in PLWH. This study was conducted in collaboration with the UAB Center for AIDS Research Network of Integrated Clinical Systems site. Custom multiplex human inflammatory assays were conducted on banked plasma specimens to measure cytokines commonly associated with chronic inflammatory pain: interleukin 1β (IL-1β), eotaxin, IL-15, IL-6, tumor necrosis factor α, and leptin. The median number of pain locations for PLWH with multi-site pain was 4, and the most common pain locations included low back, knees, head (headache), and shoulders.

Table 2. Cytokine differences between PLWH with and without chronic multi-site pain

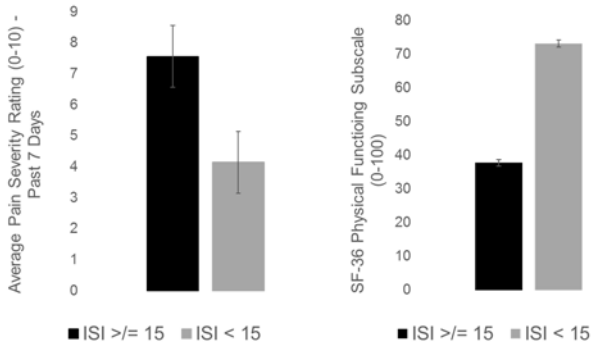
Variable	PLWH with pain (n=70)	PLWH without pain (n=70)	Sig.
Interleukin 1 – Beta (IL-1β)	0.63 (0.05 – 1.77)	0.15 (0.05 – 0.64)	**.02**
Interleukin 6 (IL-6)	0.72 (0.44 – 1.35)	0.65 (0.44 – 0.98)	.35
Tumor Necrosis Factor – Alpha (TNF-α)	2.90 (2.12 – 3.74)	2.66 (2.13 – 3.49)	.45
Eotaxin	134 (103 – 209)	126 (91 – 188)	.09
Interleukin 15 (IL-15)	2.47 (1.92 – 3.25)	2.39 (1.92 – 2.92)	.35
Leptin	20.0 (11.4 – 39.2)	18.2 (9.7 – 30.0)	.46

Note: data presented represent median levels of cytokines and interquartile range. All cytokines except for leptin were measured in pictograms per milliliter. Leptin was measured in nanograms per milliliter.

As displayed in **Table 2**, we found that PLWH with chronic multi-site pain had significantly higher median levels of IL-1β than PLWH without any pain. In Table 2, median levels of cytokines with interquartile ranges are presented to account for non-normal distributions. Although not significantly different, PLWH with chronic multi-site pain consistently demonstrated greater median levels of all other cytokines examined in this study in comparison to PLWH without pain. These findings tentatively suggest that pro-inflammation, particularly IL-1β, may be implicated in the pathogenesis of chronic pain in PLWH. These data were recently published by our investigative group (*Merlin et al. J Acquir Immune Defic Syndr. 2017, 75(4):e99-e103; doi: 10.1097/QAI.0000000000001377*).[101]

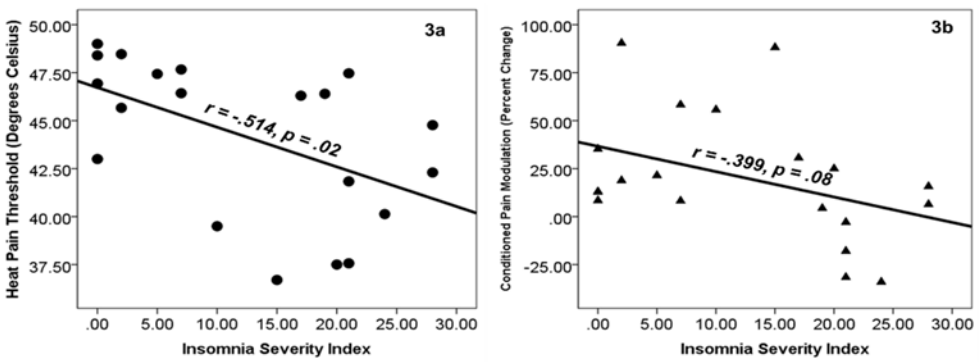
Study 3 is an ongoing pilot study currently being conducted in the laboratory of Dr. Goodin. The goal of this study is to provide initial, preliminary data highlighting whether insomnia is associated with pain sensitivity, pain in everyday life, physical function, and inflammatory biomarkers in PLWH. A total of 20 PLWH have been recruited for Study 3. Each participant completed a validated and commonly used measure of insomnia (Insomnia Severity Index), pain in everyday life (Brief Pain Inventory), and physical function (SF-36) prior to completion of an experimental pain testing battery to assess pain sensitivity. Blood was drawn before, during, and after the pain sensitivity tests to examine basal cytokines and pain-related cytokine reactivity. Previous clinical sleep research has validated that a score of 15 or greater on the Insomnia Severity Index is consistent with a moderate to severe degree of insomnia.[102] Using this cut score, it was revealed that 55% (N = 11) of the 20 PLWH in this study reported at least a moderate degree of insomnia. This percentage is consistent with previously published insomnia prevalence rates in PLWH, as well as our expectation that ~60% of PLWH recruited for this proposal will meet DSM-5/ICSD-3 criteria for chronic insomnia disorder. Of those PLWH with an Insomnia Severity Index score ≥ 15, 73% indicated that pain has been a problem every day or nearly every day for the past six months, while the remaining 27% reported that pain has been a problem at least half the days in the past six months. As can be seen in **Figure 2a and 2b**, the average severity of pain symptoms over the last 7 days is greater, while self-reported physical functioning is worse, for PLWH with moderate to severe insomnia (≥15) compared to those PLWH with normal sleep or subthreshold insomnia (<15). The Cohen's D effect sizes representing these differences are large (1.93 for pain, 1.15 for physical function) and lends support to hypotheses 2b. Greater severity of reported insomnia among PLWH was also associated with increased experimental pain sensitivity, which lends support to hypothesis 1a of this proposal. Specifically, the scatterplots presented in **Figure 3a and 3b** suggest that increasing insomnia burden is associated with decreased pain threshold and decreased capacity to endogenously inhibit pain processing (i.e., conditioned pain modulation) for PLWH. Lastly, our pilot data collected from Study 3 have begun to reveal some interesting associations among insomnia and pain-related inflammatory biomarkers in PLWH. Thus far, we have assayed IL-6 and TNF-α reactivity to the experimental pain stimuli for 14 PLWH. These cytokines were collected across 4 time-points before, during, and after the pain stimuli. As can be seen in **Figures 4a and 4b**, the inflammatory cytokine data are presented separately for PLWH with moderate to severe insomnia (≥15; N = 9) compared to those PLWH with normal sleep or subthreshold insomnia (<15; N = 5). PLWH with insomnia ≥15 demonstrated noteworthy IL-6 and TNF-α reactivity in response to experimental pain testing, and the IL-6 and TNF-α levels remained elevated at the final sampling time-point. By comparison, PLWH with insomnia <15 demonstrated an immediate increase in IL-6 and TNF-α levels following the experimental pain testing that then returned to approximate baseline levels by the final sampling time-point. The overall magnitude of IL-6 and TNF-α secretion was greater for PLWH

Figure 2a and 2b: Difference in average everyday pain severity and physical functioning between PLWH with and without insomnia



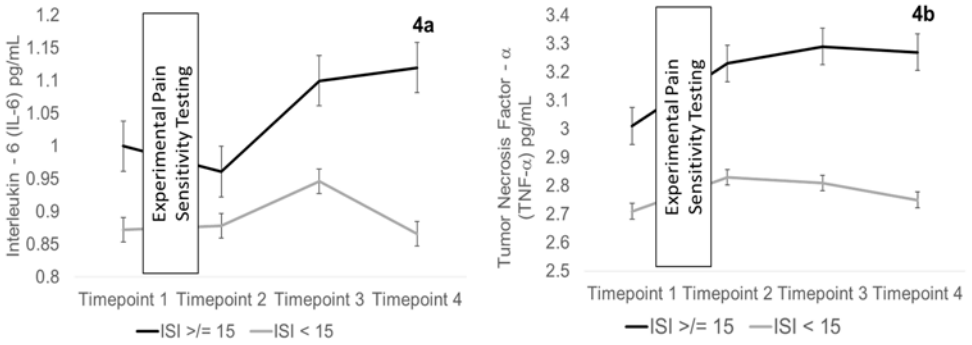
Note: ISI = Insomnia Severity Index

Figure 3a and 3b: Associations of greater insomnia severity with decreased heat pain threshold (3a) and diminished conditioned pain modulation (3b).



with insomnia compared to PLWH without insomnia. The effect sizes representing differences in IL-6 (Cohen's D = .412) and TNF-α (Cohen's D = .358) reactivity between PLWH with and without insomnia were between small and medium in size according to Cohen's guidelines.

Figure 4a and 4b: Differences in IL-6 (4a) and TNF-α (4b) reactivity following experimental pain testing between PLWH with insomnia (ISI >/= 15) and without insomnia (ISI < 15). ISI = Insomnia Severity Index.



C.3. Summary of Preliminary Data. These preliminary data generated from previous pilot studies conducted by our research team are important to the current proposal for several reasons. 1) This previous work demonstrates the ability of our research team to work together in a collaborative and productive manner. 2) Our previous pilot work supports the feasibility and capacity of our team to collect all of the necessary data and variables included as part of the current proposal. 3) The findings revealed by our team's previous work provide proof of concept for the specific aims included in this proposal. What is currently needed is a larger, appropriately powered study to confirm the findings of our pilot work, and we propose such a study here.

C.4. Participants. According to our power analysis (section F.1.1. below), we will recruit a total of 240 adults (120 PLWH, 120 non-HIV). It is anticipated that at least 50% (60) of the 120 PLWH who complete the Specific Aim 1 protocol will meet DSM-5/ICSD-3 criteria for chronic insomnia disorder, while the remaining 60 PLWH will not. Additionally, we will include 60 non-HIV with insomnia and 60 non-HIV without insomnia. Because the protocol developed to address Specific Aim 1 will only include a single (approximately 3-hour long) study session, minimal attrition is expected for this portion of the study based upon the preliminary work of the PI and research team. This should result in a final sample size of 240 participants who complete the protocol developed to address Specific Aim 1. To address Specific Aim 2, the 60 PLWH with insomnia along with the 60 non-HIV with insomnia will be included. It is expected that ~17-20% of the sample will drop out before completing these longitudinal procedures, resulting in a final sample size of 100 (50 PLWH, 50 non-HIV) with insomnia who complete the protocol developed to address Specific Aim 2. Enrollment will begin almost immediately after funding is awarded because most of the protocols and procedures included in this proposal have already been established as part of the pilot work previously completed by the PI.

C.5. Recruitment. With permission from the clinic director (see Dr. Raper's letter of support), PLWH will be recruited from the UAB 1917 HIV Clinic Cohort using posted study flyers and pamphlets. The 1917 HIV Clinic at UAB currently provides health services to approximately 3,300 PLWH in the Birmingham area and greater Alabama. Non-HIV participants with insomnia will be recruited from the UAB Sleep/Wake Disorders Center with the assistance of Dr. Thomas (co-investigator). Individuals without HIV or insomnia will be recruited from the local Birmingham community surrounding UAB. Interested participants will call a member of the research team to initiate study screening and determine eligibility. We plan to receive ample assistance from the UAB Center for AIDS Research (CFAR) in recruitment and retention of PLWH.

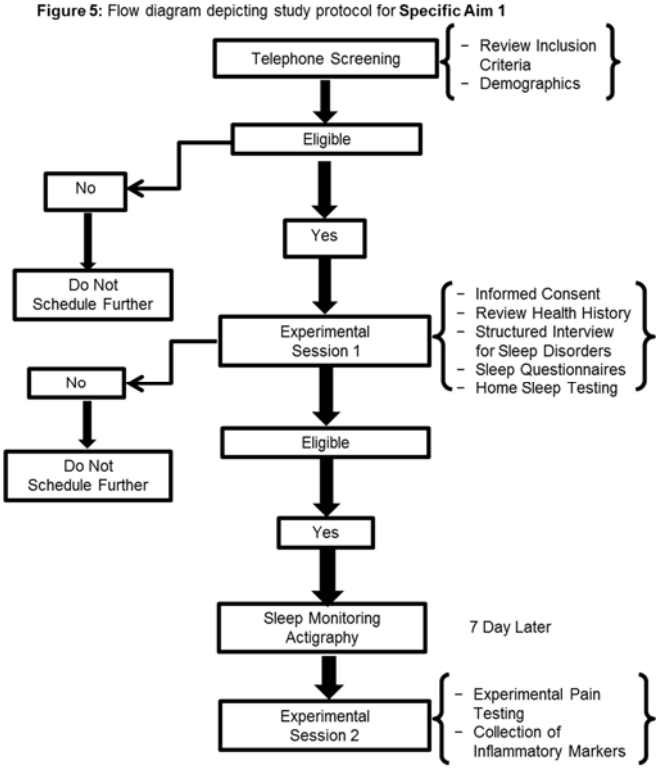
C.6. Initial Telephone Screening and Medical Record Review. All PLWH and non-HIV participants will complete a telephone screening interview to determine initial study eligibility. For PLWH, this will also involve a review of each participant's UAB electronic medical record to confirm HIV status and determine approximate duration of HIV infection, current and past treatment regimens for HIV, comorbid health conditions, and current medication use. All PLWH must be currently receiving stable antiretroviral therapy (ART) for inclusion in this study. Given that PLWH will be recruited from an HIV treatment clinic, it is reasonable to assume that many may be receiving medications that could affect sleep (e.g. efavirenz, INSTIs, Benzos, etc.) Similarly, the non-HIV insomnia group may also be receiving medication for sleep. We will not exclude participants based upon medication use as this could seriously hinder recruitment efforts or otherwise bias our sampling. We are aware that both continued use and temporary withdrawal from these medications (should we ask participants to withhold) could affect sleep and pain perception. Therefore, participants will not be asked to withhold medications during study enrollment. Rather, all medications currently prescribed that could affect sleep and/or pain will be recorded and controlled in statistical analyses as needed. Participant enrollment will be delayed if they had recent

changes (past 60 days) in any of their medications that could affect sleep; after 60-days post-change they can then be enrolled.

D.1. Specific Aim 1 Methods. The protocol for Specific Aim 1 will be carried out using laboratory space and resources provided by the UAB Clinical Research Unit (CRU), which is supported by the UAB Center for Clinical and Translational Science and an NIH Center for Translational Science Award (CTSA; UL1TR000165). According to the flow diagram in **Figure 5**, participants will complete two experimental study sessions as well as 7 days of actigraphy and sleep diary collection.

D.2. Experimental Session 1. Review of health history will be completed and blood pressure monitored to ensure inclusion criteria continue to be met. Please refer to "Human Subjects Protections" document for full list of exclusion criteria. All participants will then complete the ***Diagnostic Interview for Sleep Patterns and Disorders (DISP)***.[103] The DISP was developed to assess sleep disorders in clinical samples in non-sleep specialty settings according to diagnostic guidelines put forth by the International Classification of Sleep Disorders, second edition (ICSD-3). PLWH who meet DISP criteria for chronic insomnia disorder (≥3 days/week for 3 consecutive months) will be included in the study, as well as those PLWH who do not meet criteria for any sleep disorder. PLWH who meet criteria for a sleep disorder other than insomnia (i.e., not insomnia) will be excluded. It is anticipated that the non-HIV group with insomnia will meet DISP criteria for insomnia. Those without HIV or insomnia will be included for further participation only if they do not meet any DISP criteria for a sleep disorder. Participants will also complete the following validated measure of insomnia burden. The ***Insomnia Severity Index*** **(ISI)** is designed to be both a brief screening measure of insomnia and an outcomes measure for use in treatment research.[104] Scale content corresponds in part to DSM-5/ICSD-3 criteria for insomnia, and measures the participant's current (within the past 2 weeks) perception of symptom severity, distress, and daytime impairment. Previous clinical sleep research has validated that a score ≥15 on the ISI is consistent with a moderate to severe degree of insomnia.[102] Lastly, all participants will complete ***Home Sleep Testing (HST)*** the night of Experimental Session 1 using a Resmed ApneaLink Air device (Resmed, San Diego, CA). This device is a 5 channel (respiratory effort, pulse, oxygen saturation, nasal airflow, and snoring) portable monitoring system that has been validated against monitored, laboratory-based polysomnography.[105] HST will measure airflow (i.e., nasal pressure) using a nasal cannula and oxygen saturation to identify apnea and hypopnea and calculate an apnea hypopnea index (AHI; number of apnea and hypopnea per hour). Participants with suspected obstructive sleep apnea (AHI >15/hr) will be excluded from further participation to help reduce insomnia secondary to probable sleep apnea. <u>The behavioral sleep specialist for this study (Dr. Thomas) will oversee all aspects of sleep data collection including actigraphy, HST, DISP, and ISI.</u>

Figure 5: Flow diagram depicting study protocol for **Specific Aim 1**



D.3. Sleep Monitoring and Actigraphy (7 days between experimental sessions 1 and 2).

<u>D.3.1. Actigraphy.</u> Objective sleep data will be acquired using the Actiwatch2 (Respironics, Bend, OR), a wrist-worn, watch-like actigraph. The Actiwatch2 device is a solid-state piezo-electric accelerometer that collects data on activity (i.e., arm motion) and ambient light. Actigraphy will be conducted to assist in identifying sleep/wake periods, as well as providing objective sleep data including total sleep time, mid-sleep time (the mid-time point between bed time plus falling asleep time and the wake-up time), sleep latency, awakenings after sleep onset, and sleep efficiency. The Actiwatch2 has good reliability and criterion validity.[106,107] Actigraphy has been shown to be comparable to polysomnography[94] and studies have demonstrated the validity of actigraphic measurement in persons with and without chronic insomnia disorder.[108,109] Dr. Thomas will oversee processing, quality control, and analyses of these data consistent with current methodological standards.[110]

D.3.2. Daily diaries. Participants will monitor and report on their sleep between the two experimental sessions in real-time using a pencil-and-paper consensus sleep diary.[111] This will be done in conjunction with the actigraphic measurement of their sleep to improve the quality of the actigraphy data. Diaries will be completed twice per day, before going to bed at night, and then again the following morning, to provide a measure of participants' self-reported sleep patterns and quality. In addition to sleep and napping behavior, the daily diaries will also include questions related to pain and mood as well as alcohol, caffeine, and nicotine intake throughout the day, and medication use.

D.4. Experimental Session 2. Sessions will be conducted starting between 9 and 11am to control for circadian variation in cytokine levels.[112] Blood will be drawn five times, before, during and after the experimental pain testing battery to specifically examine inflammatory responses to the painful stimuli. Following completion of the experimental pain testing battery, and while they are waiting for the remaining blood to be drawn, participants will complete study measures to obtain self-reported information regarding recent pain experiences, as well as mood disturbances including depression and anxiety. The ***Patient-Reported Outcomes Measurement Information System (PROMIS)*** pain intensity, pain interference, and pain behavior items will be used for this study.[113-115] For instance, patients will be asked to rate the intensity of their pain at its "worst" and "on average" over the past 7 days as well as the intensity "right now". The ***Center for Epidemiological Studies – Depression Scale (CES-D)*** is a 20-item measure of symptoms of depression that has been shown to be reliable and valid in both general and clinical populations.[116] The CES-D will be used to characterize study participants with respect to depressive symptoms. The ***State-Trait Anxiety Inventory (STAI) – Trait Version*** will be used to assess individuals' relatively enduring disposition to feel stress, worry, and discomfort.[117] **Figure 6** portrays the temporal precedence of procedures to be completed by participants for experimental session 2.

D.4.1. Experimental pain testing. A multi-faceted experimental pain testing battery will be used in accordance with the protocols previously developed and refined by our group for the assessment of pain sensitivity.[38,118,119] Experimental pain testing is a reliable and valid method to assess pain sensitivity without tissue damage, and it has demonstrated clinical pain relevance.[99,120] The use of experimental pain testing for measuring pain sensitivity often includes a multimodal, multitissue approach whereby different stimulus modalities (e.g., heat, cold, and pressure) are applied to different tissues (e.g., skin, muscles, and viscera). We will assess the pain sensitivity response measures listed below and in **Table 3**:

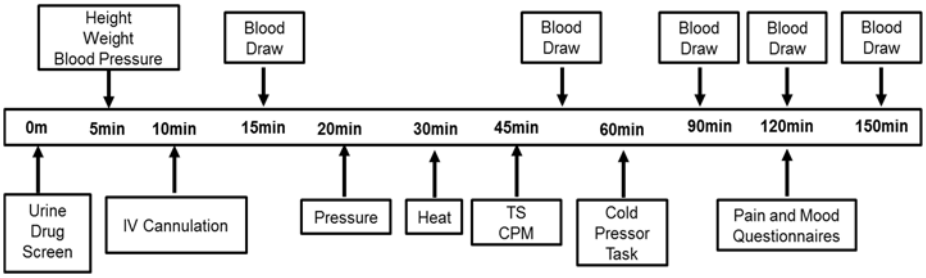


Figure 6: Time line for participant matriculation through experimental session 2. Note: TS = temporal summation, CPM = conditioned pain modulation.

***Pain threshold*:** refers to the intensity at which a stimulus is first perceived as painful.

***Pain tolerance*:** refers to the maximum amount of pain produced by a stimulus that a person is willing to tolerate.

***Suprathreshold pain responses*:** are ratings of pain in response to discrete stimuli with intensities above pain threshold detection. Patients provide an intensity rating using any number on 0-100 scale whereby 0 = no pain and 100 = the most intense pain imaginable.

Conditioned pain modulation (CPM): is a routinely used pain testing protocol for the measurement of endogenous pain inhibition. CPM refers to the reduction in pain from one stimulus (the test stimulus) produced by the application of a second pain stimulus at a remote body site (the conditioning stimulus).[121]

Temporal summation (TS) of pain: refers to a form of endogenous pain facilitation characterized by the

Table 3. Types of experimental pain testing stimulus modalities, the tissues they stimulate, and the measures of pain sensitivity that are captured by each modality.

Stimulus modality	Tissue stimulated	QST response measures
Thermal (contact heat)	Cutaneous	Pain threshold Pain tolerance Suprathreshold pain responses Temporal summation of pain
Thermal (immersion cold)	Cutaneous Myofascial	Pain threshold Pain tolerance Suprathreshold pain responses
Mechanical (pressure)	Cutaneous Myofascial	Pain threshold Pain tolerance Suprathreshold pain responses Temporal summation of pain
Conditioned Pain Modulation	Cutaneous Myofascial	Conditioned pain modulation is often measured with cold (immersion) as the conditioning stimulus and heat or pressure (contact) as the test stimulus

perception of increased pain despite constant or even reduced peripheral afferent input.[122]
We hypothesize that PLWH with insomnia will demonstrate ↓pain threshold, ↓pain tolerance, ↓conditioned pain modulation, ↑temporal summation (i.e., all indicators of enhanced pain sensitivity) compared to PLWH without insomnia and the non-HIV groups with and without insomnia. For the final aspect of the experimental pain testing battery, participants will be instructed to immerse their dominant hands into a cold water bath maintained at 4^0C for as long as possible (however, they can discontinue at any time). The cold water immersion task has previously been shown to be effective for eliciting a pro-inflammatory response.[119,123]

D.4.2. Inflammatory marker assays. The Meso Scale Discovery (MSD) method is an enzyme-linked immunosorbant assay (ELISA) that uses electrochemiluminescence as the signal to detect binding events.[124] Conducting the MSD-based assay is similar to conducting any ELISA; however, the MSD system offers sensitive analyses with a greater dynamic range than other ELISA and RIA approaches. The use of an MSD imager utilizes antigen-antibody technology, however, rather than measuring absorbance with a spectrophotometer an instrument is used that measures light emitted upon electrochemical stimulation or electrochemiluminescence. The advantage of this technology is that it allows for multiplexing, or the measurement of more than one biomarker at a time from one sample. Therefore, MSD will be used for the quantification of pro-inflammatory (TNF-α, IL1-β, IL-6, IL-12, IL-18, C-reactive protein, sCD14/163, D-dimer, and IFN-gamma), as well as anti-inflammatory (IFN-alpha, TGF-beta, IL4, IL-10, and IL-13) responses to pain testing (Aim 1) and weekly changes related to insomnia burden (Aim 2). Multiplex assays have been shown to be reliable for assessment of inflammatory biomarkers in HIV.[125]

E.1. Specific Aim 2 Methods. This study aim will be addressed by including groups of PLWH and non-HIV individuals who both meet criteria for chronic insomnia disorder according to the DISP (section D.2. above), and following them for six consecutive weeks. These two groups with insomnia identified during completion of Specific Aim 1 methods will wear actigraphy devices and complete daily sleep and pain diaries. Sleep monitoring and daily diaries will be completed for 7 consecutive days, after which blood will be drawn to evaluate inflammatory markers. Physical functioning assessments will then be completed. These procedures will be completed at the same time every week across the 6 consecutive weeks as shown in **Figure 7**.

E.2. Longitudinal Sleep Measurement. Previous research documenting monthly changes in sleep/insomnia status over a 12-month period has revealed significant month-to-month variability in sleep patterns and insomnia severity.[126,127] For example, in a subgroup of adults with insomnia symptoms at baseline, 88.3% reported improved sleep (i.e., became good sleepers) at least once over the 12 monthly assessments, while 27.7% reported that their sleep worsened.[126] For this proposal, the sleep of PLWH and non-HIV individuals both with insomnia will be repeatedly measured using actigraphic sleep monitoring and sleep diaries (see D.3.1. and D.3.2.) across 6 consecutive weeks. This 6-week timeline will ensure that sleep measurement occurs across consecutive months, which maximizes the potential to observe fluctuations in insomnia burden.

E.3. Daily Pain Assessment. As part of the daily sleep diaries that will be completed for 7 consecutive days, each week for 6 consecutive weeks, PLWH with insomnia will also provide daily ratings of pain. Again, the ***Patient-Reported Outcomes Measurement Information System (PROMIS)*** pain intensity, pain interference, and pain behavior items will be used (see D.4.) by adding them to the daily sleep diary for completion each day prior to going to bed. Upon returning to the laboratory at the end of each 7-day sleep (and pain) monitoring period, participants will also complete the ***Short Form-McGill Pain Questionnaire (SF-MPQ).***[128] The SF-MPQ is a validated measure that allows for quantitative, multidimensional pain ratings to be obtained in a brief period of time.

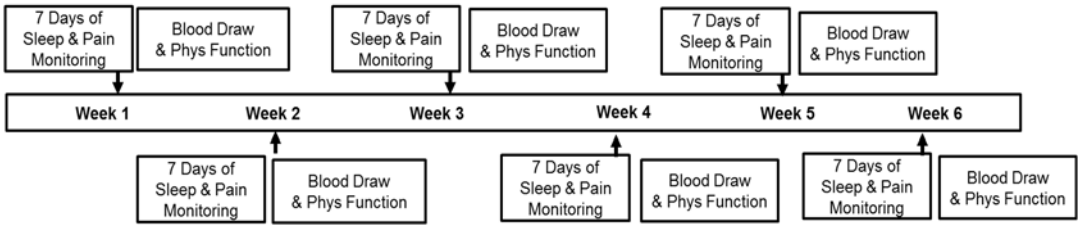


Figure 7: Time line for PLWH with insomnia to matriculate through study protocol for **Specific Aim 2**.

E.4. Repeated Quantification of Systemic Inflammatory Markers. At the end of each 7-day sleep monitoring period, participants will return to the laboratory in order to hand over their actigraphs and daily sleep and pain diaries. They will complete several additional study questionnaires including the Insomnia Severity Index, the

Center for Epidemiological Studies-Depression Scale, and the State-Trait Anxiety Inventory – Trait Version. After completing these measures, blood will be drawn and processed for subsequent assay of inflammatory markers. *As described in D.4.2., the Meso Scale Discovery (MSD) method will be carried out in order to quantify levels of pro- and anti-inflammatory markers across the six consecutive weeks.* This will be done to compare Inflammatory marker levels following weeks of high insomnia burden to levels following weeks of low insomnia burden.

E.5. Physical Function Measures. After blood draw, participants will then complete a series of standardized physical functioning measures including a Short Physical Performance Battery and Timed Up and Go Test. The ***Short Physical Performance Battery (SPPB)*** consists of three measures of lower-extremity function: standing balance, 4-meter walking speed, and ability to rise from a chair. These measures have been standardized and are widely used in clinical populations as measures of lower extremity function. The ***Timed Up and Go test (TUG)*** is a simple test used to assess a person's mobility and requires both static and dynamic balance. It measures the time that it takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. Any pain experienced during completion of the physical functioning measures will be assessed using the 0-100 numeric rating scale. At the end of each session, the actigraph will be reconfigured, charged, and handed back to the participant to monitor the upcoming week's sleep.

F.1. Statistical Methods. Power analysis and development of the analytic plan for Specific Aims 1 and 2 was completed with assistance from Dr. Dustin Long, the biostatistician co-investigator for this application.

F.1.1. Specific Aim 1. For this aim, we assumed an effect size of 0.25, which is smaller than those observed in our preliminary data (Cohen's D range of 0.35 to 0.77). This effect size was selected to ensure that this study would be appropriately powered even if our previous work overestimated the true effect size. We do not assume that there will be an interaction effect between HIV and insomnia status, but rather an additive effect. The additive model assumes that the excess-risk for two factors (e.g., HIV and insomnia) operating simultaneously is equal to the excess risk for the first factor plus the excess risk for the second factor. Thus, our statistical model for examining the impact of insomnia on pain, inflammation, and physical function in PLWH is a factorial ANCOVA. We set our individual test Type 1 error at 0.025, which is a Bonferroni corrected value based on two tests (HIV and insomnia status) and overall Type 1 error of 5%. With these assumptions and 90% power, we will need 200 participants total with 50 participants in each group created by combining HIV and insomnia status (50 PLWH with insomnia, 50 PLWH without insomnia, 50 non-HIV with insomnia, and 50 non-HIV without insomnia) (**Table 3**). A total of 240 participants will be recruited to allow for 20% attrition.

Data analysis will begin with calculating and comparing measures of central tendency (sample mean, sample median) and dispersion (sample variance, interquartile range) for all measures of pain sensitivity (e.g., threshold, tolerance, temporal summation, conditioned pain modulation) and markers of inflammatory reactivity. Non-normally distributed data will be transformed using a logarithmic function as needed. Differences in pain sensitivity (*hypothesis 1a*) adjusting for confounding factors will be examined using analysis of covariance (ANCOVA). Post-hoc pairwise contrasts amongst groups (PLWH with and without insomnia, non-HIV individuals with and without insomnia) will be completed correcting for multiple comparisons, as presented in the sample size calculation. Additionally, linear mixed models (LMMs), containing at least random intercepts and time slopes per participant, will be employed to examine inflammatory cytokine reactivity to the painful stimuli (*hypothesis 1b*). Additional fixed effects (up to cubic polynomials) will be included to determine associations among pain sensitivity and inflammatory marker reactivity.

F.1.2. Specific Aim 2. It is anticipated that the 120 participants with insomnia (60 PLWH, 60 non-HIV) identified through Specific Aim 1 will matriculate through this portion of the protocol. Allowing for 20% attrition over the course of the 6-week observation period, we anticipate that 100 participants will complete all procedures included in Specific Aim 2. Using the methods of Diggle et al.[129], this sample size would allow us to detect a difference in slopes of 0.25 of a standard deviation with 90% power. For example, we can detect a difference in the linear association of pain severity and time between PLWH with insomnia and non-HIV individuals with insomnia of 1.5 (0.25 times a standard deviation of 6.[104]

Generalized linear mixed models (GLMMs) will be performed to address the hypotheses for Specific Aim 2. For data that appear normally distributed, LMMs will be used and the appropriate GLMM will be used for non-normal outcomes. Associations between time and outcomes (pain severity, inflammation, physical function) will be compared between PLWH and non-HIV participants with insomnia according to time by group interactions (*hypothesis 2a*). Insomnia burden for each week of the study will be categorized as "high" and "low" burden and a main effect for this designation and interaction with HIV status will be included in a model for each outcome

(*hypothesis 2b*). Lastly, inflammatory marker (previously outcomes) associations with pain severity and physical functioning will be assessed in separate models (*hypothesis 2c*). All models will include potential confounders as appropriate and all assumptions for LMMs or GLMMs will be assessed. No changes in these analyses are planned due to missing data as both types of models are appropriate when data are missing-at-random.

G.1. Potential Obstacles and Alternative Approaches. 1) Challenges of longitudinal research: Attrition is always a concern in longitudinal studies, and we have planned for 20% attrition over the 6-week period for Specific Aim 2. However, the research team has experience with longitudinal studies (e.g., Goodin; R37AG033906 and Younger; R01AI107655), and we expect to achieve high levels of retention by maintaining frequent contact with participants. 2) Directionality of associations among insomnia, pain, and inflammation: We propose here that insomnia will drive pain and inflammation in PLWH; however, it stands to reason that over time pain experiences and inflammation could feedback to insomnia to worsen its severity. Clinically, it is common for insomnia to promote heightened pain the next day, and for this heightened pain to beget greater insomnia severity the following night.[39] Our data analytic approach presented for Specific Aim 2 will allow us to model temporal associations among insomnia burden, pain, and inflammation, which will allow us to confirm whether insomnia is driving pain and inflammation in PLWH, or vice versa. 3) Inflammatory markers: It is possible that the proposed inflammatory markers may not reveal the hypothesized group differences by HIV and insomnia status. We will process blood and quantify inflammation in waves, rather than waiting until all blood is collected and assaying at the end of the study. This will allow us to appreciate whether group differences in inflammatory markers are emerging as hypothesized. If we do not see differences early on, we will consult with our team's inflammation expert (Dr. Younger) and identify alternative inflammatory markers to collect and assay. We will collect excess blood from each participant so that any alternative biomarker can still be obtained from stored blood for all participants. As such, statistical power for data analyses including inflammatory biomarkers will be preserved. 4) Insomnia phenotypes: Different phenotypes of sleeplessness can be distinguished as part of the chronic insomnia disorder diagnosis, including sleep-onset insomnia (trouble falling asleep), sleep-maintenance insomnia (trouble staying asleep), and a combination of the two.[127] Within our PLWH and non-HIV groups with insomnia, we will classify participants according to these phenotypes as part of exploratory data analyses to determine whether a specific insomnia phenotype(s) is more related to pain, inflammation, and physical function compared to others.

H.1. Timeline and Benchmarks for Success. Table 4 includes start-up, benchmarks by aim, manuscript submission, and submission of a subsequent R01 to further build upon our program of research addressing insomnia in PLWH.

Table 4: Timeline of the 5 year project and benchmarks for success

	Year 1	Year 2	Year 3	Year 4	Year 5
Participant recruitment target	30 PLWH 15 non-HIV	60 PLWH 30 non-HIV	60 PLWH 30 non-HIV	60 PLWH 30 non-HIV	30 PLWH 15 non-HIV
Study start-up					
Hire & train staff	XX				
Obtain final regulatory approval	XX				
Study procedures					
Participant recruitment	XX	XX	XX	XX	XX
Facilitate Aim 1 and Aim 2 protocols	XX	XX	XX	XX	XX
Assay batches	XX	XX	XX	XX	XX
Analysis/Dissemination					
Begin data cleaning, analysis			XX		
Submit first abstract/manuscript for each study aim			XX	XX	XX
Study Completion					
Submit additional abstracts/manuscripts					XX
Submit subsequent R01 application					XX

J.1. Future Directions. The findings generated from this study will lay the foundation for a programmatic line of research aimed at better understanding the downstream health consequences of insomnia in PLWH, particularly the impact of insomnia on pain and inflammation. If insomnia is indeed found to be a driver of pain, inflammation, and poor physical functioning in PLWH, we will subsequently propose a clinical trial as part of a competing R01 renewal to determine whether a psychologically-based intervention (cognitive behavioral therapy for insomnia) not only improves sleep in PLWH, but also pain, inflammation, and function. Initial pilot data demonstrating feasibility and proof of concept will be gathered in collaboration with Dr. Thomas within his Behavioral Sleep Medicine Program at the UAB Sleep/Wake Disorders Clinic. Efforts are currently underway to collect these pilot data.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

Are Human Subjects Involved	● Yes ○ No
Is the Project Exempt from Federal regulations?	○ Yes ● No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	The Impact of Insomnia on Pain, Physical Function, and Inflammation in HIV	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

The Impact of Insomnia on Pain, Physical Function, and Inflammation in HIV

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	● Yes	❍ No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

2.2. Eligibility Criteria

2.3. Age Limits	Min Age: 18 Years	Max Age: 85 Years
2.4. Inclusion of Women, Minorities, and Children	R01_Women_and_Minorities_Children.pdf	
2.5. Recruitment and Retention Plan	Recruitment_and_Retention.pdf	
2.6. Recruitment Status	Not yet recruiting	
2.7. Study Timeline		
2.8. Enrollment of First Subject	12/01/2018	Anticipated

Inclusion of Women and Minorities

No restrictions will be issued to the inclusion of women or minorities in this proposal. Therefore, we anticipate recruitment of these groups to be reflective of the patient population currently receiving treatment at the UAB 1917 HIV Clinic.

Inclusion of Women
According to recent data, women represent approximately 56% of patients at the 1917 HIV Clinic. Selection of the study population will be independent of sex/gender. Furthermore, in our recent pilot study we successfully recruited 6% transgender women. No recruitment restrictions will be made according to transgender status. Our study staff have experience with enrolling women into HIV-related research and will be adequately trained to answer questions regarding study procedures and participation. We anticipate enrolling a relatively balanced proportion of men and women into this study.

While our main focus is investigating the impact of insomnia on pain, physical function, and inflammation, we will also explore potential sex differences in the patterns of associations among these variables. We have a documented record of research on sex differences in pain (**see below**). Therefore, we will include sex as a factor in our models analyzing the impact of insomnia, and we will conduct sex-stratified exploratory analyses to identify potential sex-specific associations among insomnia, pain, physical function, and inflammation.

Bulls, H. W., Freeman, E. L., Anderson, A. J., Robbins, M. T., Ness, T. J., & Goodin, B. R. (2015). Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. *Journal of Pain Research*, 8, 311.

Goodin, B. R., McGuire, L., Allshouse, M., Stapleton, L., Haythornthwaite, J. A., Burns, N., ... & Edwards, R. R. (2009). Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. *Journal of Pain*, 10(2), 180-190.

Inclusion of Minorities
According to recent data, minority representation within the UAB 1917 HIV Clinic includes 59% African American and 0.2% Hispanic; the remainder are White. Notably, an even higher proportion of individuals who identify as African American (80%) participated in our pilot study at UAB. There are very few Hispanic patients at the 1917 Clinic, and even fewer Asian, Pacific Islander, Native American, or other. Therefore, we anticipate that our study will be comprised of non-Hispanic African Americans and Whites. Selection of participants for inclusion in the study, however, will be completely independent of ethnicity or race.

The expected racial and sex distributions of our population are presented in the Targeted/Planned Enrollment Table.

Inclusion of Children

In general, the UAB 1917 HIV Clinic does not provide care to children. However, this clinic does provide care for patients as young as 18 years. Therefore, young adults who are 18 years or over will be eligible for study participation, although there are no specific recruitment strategies for inclusion of these patients. Children less than 18 years of age will not be included in this study given that the primary aim is to examine the impact of insomnia on pain and inflammation in adult persons living with HIV. In the state of Alabama, 18 is the age when individuals are legally able to provide informed consent for research participation.

Recruitment and Retention

Recruitment and informed consent. The following measures will be taken to adequately address recruitment and informed consent for this study.

1. **Informed consent.** The proposed study will be approved by the UAB Institutional Review Board. All potential participants will be informed of the nature of the procedures and associated risks. Also, they will be informed that they can withdraw from the study at any time and this will have no adverse impact on the study or on their own future medical treatment. Subsequently, if they are still interested, they will be informed about HIPPA regulations and asked to review and sign an informed consent form to grant authorization for collection of protected health data. The informed consent will be reviewed in detail with each potential participant, and they will be provided a copy of the informed consent for their personal records. Informed consent will be documented in writing via the participant's and investigator's signatures.
2. **Recruitment.** Participants will be recruited from the UAB 1917 HIV Clinic. Data from the 1917 Clinic indicates that approximately 3,000 PLWH are actively receiving treatment at this facility. Our clinic-based recruitment methods are likely to yield substantial numbers of PLWH willing to participate in the study. PLWH with insomnia will be paid $550 for completing the entire protocol included in Specific Aims 1 and 2. PLWH without insomnia and controls will be paid $250 for completing the protocol included as part of Specific Aim 1. PLWH without insomnia and controls will not matriculate through the protocol developed for Specific Aim 2. This reimbursement is comparable to what others who have conducted similar studies provide participants for their efforts, based upon the time commitment and number of sessions. We have a great deal of experience recruiting participants for these types of procedures. Due to our clinic-based recruitment efforts, we anticipate no difficulty in achieving our proposed enrollment. Indeed, these methods were quite successful during our previous pilot work.
3. **Retention.** We are over-enrolling by 20% to account for attrition, particularly during the protocol addressing Specific Aim 2. Therefore, 120 PLWH and 120 non-HIV individuals will be recruited with the expectation that all 240 will complete the protocol for Specific Aim 1. Of these 120 PLWH, it is expected that 60 (50%) will meet DSM-5 criteria for insomnia. These 60 PLWH with insomnia along with 60 non-HIV with insomnia will continue to matriculate through the study protocol by completing the study procedures included as part of Specific Aim 2. Here we anticipate ~17% attrition, which will result in a final sample of 100 (50 PLWH, 50 non-HIV) with insomnia finishing the study. The anticipated attrition rates are consistent with the pilot work completed to inform this application as well as other studies previously completed by the PI. The final sample size of 240 participants for Specific Aim 1 and 100 participants for Specific Aim 2 will ensure adequate statistical power for detecting the hypothesized effects. In order to maximize retention, we will maintain frequent contact with participants. We will send messages to participants on a weekly basis, either by email or telephone, thanking them for their participation and reminding them of future appointments. *Our study team at UAB will receive assistance from the UAB Center for AIDS Research (CFAR) for recruitment and retention of PLWH.*

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ❍ Yes ● No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s):

Comments: Total planned enrollment is 120 persons living with HIV (60 with insomnia, 60 without insomnia) and 120 non-HIV persons (60 with insomnia, 60 without insomnia) for a total of 240 participants overall.

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	54	54	6	6	120
White	54	54	6	6	120
More than One Race	0	0	0	0	0
Total	108	108	12	12	240

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	0	0	0	0	0	0	0	0	0	0
White	0	0	0	0	0	0	0	0	0	0
More than One Race	0	0	0	0	0	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	R01_Human_Subjects_Protections-V2.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	❍ Yes ● No ❍ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	Data_and_Safety_Monitoring_Plan.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	

Protection of Human Subjects

Human Subjects Involvement and Characteristics: A total of 120 PLWH (approximately 50-60% with chronic insomnia) and 120 non-HIV individuals (50% with chronic insomnia) between 18 and 85 years of age will be enrolled. Enrollment will begin almost immediately after funding is awarded because most of the study policies and procedures have already been established as part of the pilot work previously completed by the PI. The inclusion criteria for PLWH include the following. 1) Confirmed HIV diagnosis and currently a patient in the UAB 1917 HIV Clinic. 2) Age 18 – 85; the lower end of this age range was chosen in order to capture young adults with HIV infection, and participants over 85 years are increasingly likely to meet one or more exclusion criteria. 3) All PLWH must be currently receiving stable antiretroviral therapy (ART) for inclusion in this study. 4) PLWH with insomnia must meet DSM-5 diagnostic criteria for insomnia including sleep difficulty that occurs at least 3 times per week and has been a problem for at least 3 consecutive months. 5) PLWH without insomnia must not meet criteria for insomnia or any other sleep disorder as determined by the Diagnostic Interview for Sleep Patterns and Disorders (DISP). 6) Non-HIV participants must be confirmed as HIV negative. Those with insomnia will meet the same diagnostic criteria for chronic insomnia disorder as the PLWH. Non-HIV without insomnia must not meet any criteria for sleep disorder or insomnia. Participants will be excluded if they have any concurrent medical conditions that could confound interpretation of sleep, pain, and/or inflammatory measures or coexisting disease that could preclude successful completion of the protocol including:

1. Systemic rheumatic disease/condition (e.g. rheumatoid arthritis, systemic lupus erythematosus, fibromyalgia). These rheumatologic conditions will be excluded due to their auto-immune characteristic.
2. Cachexia (wasting syndrome) and severe frailty as determined by Groningen Frailty Index (score >4) This exclusion is in place to protect against the stress of experimental pain testing.
3. A history of clinically significant surgery in the past year.
4. Uncontrolled hypertension (i.e. SBP/DBP of > 150/95), cardiovascular or peripheral arterial disease. These exclusions are in place primarily for safety reasons, because the cold pressor task represents a cardiovascular challenge. However, uncontrolled hypertension can also affect pain perception, which is another reason for excluding these individuals.
5. Poorly controlled diabetes (HbA1c > 8%) for both safety reasons, and because diabetic neuropathy could alter pain perception.
6. Neurological disease (e.g. Parkinson's, multiple sclerosis, epilepsy).
7. Serious psychiatric disorder requiring hospitalization within the past 12 months or characterized by active suicidal ideation. Any participant deemed to be actively suicidal upon study screening will be escorted to the UAB emergency room and evaluated by the Psychiatry Service.
8. Diminished cognitive function that would interfere with understanding of study procedures. The Mini-Mental Status Exam (MMSE) will be administered to ensure that participants are free of cognitive impairment that would compromise study participation.
9. Evidence for obstructive sleep apnea according to Home Sleep Monitoring.

We will not withdraw (or exclude) participants from medications that may affect sleep or pain management, but instead only include those who are stable on these medications for at least 60 days. We are aware that both continued use and temporary withdrawal from these medications (should we ask participants to withhold) could affect sleep and pain perception. Therefore, all medications currently being used for at least the past 60 days will be recorded and controlled in statistical analyses as needed.

Detection of Insomnia or other Sleep Disorders

Home sleep testing will be completed and participants with evidence of obstructive sleep apnea will be dismissed from the study. However, this information will be relayed back to the participant's primary care physician for care coordination. Additionally, these individuals will be provided with a referral to the UAB Sleep/Wake Disorders Clinic for initiation of care, which will be coordinated by Dr. Thomas (study co-I). In the event that a participant is not receiving treatment for insomnia, and when a suspected new case of insomnia is detected, treatment will also be offered and coordinated with other providers. Given that the time from referral to initial visit in the Sleep/Wake Disorders Clinic is approximately 6-8 weeks, participation in this study is not expected to delay access to care.

Sources of Materials

All participants will provide self-report to initially determine eligibility according to HIV status as well as recent sleep disturbances consistent with insomnia, any experiences of pain symptoms, and other co-occurring medical conditions. Study staff will then go through each participant's electronic medical record to confirm HIV diagnosis and determine whether participant is currently receiving a stable regimen of antiretroviral therapy. We will also confirm the presence or absence of other medical conditions that would warrant study exclusion. There are a total of 2 experimental sessions that make up the methodological protocol for Specific Aim 1. These two experimental sessions occur before and after 7 consecutive nights of sleep monitoring. During the first experimental session, participants will complete a Diagnostic Interview for Sleep Patterns and Disorders (DISP) in addition to several validated self-report measures of sleep quality and insomnia. These procedures will be carried out to determine who meets criteria for insomnia. These procedures will also help rule out participants with a sleep disorder other than insomnia. Following the first experimental session, participants will return home and complete 7 consecutive nights of sleep monitoring using actigraphy and nightly sleep diaries. After home sleep monitoring, all participants will return for the second experimental session. During this session they will complete an experimental pain testing battery to examine their pain sensitivity. They will provide self-report data regarding their current pain intensity and experiences of daily aches and pains over the prior three months using chronic pain measures, and several psychosocial measures will be administered that assess depressive symptoms and anxiety. Blood will be collected before, during, and after the experimental pain testing for the assessment of inflammatory biomarkers.

Following the second experimental session, only PLWH with insomnia and non-HIV individuals with insomnia will be asked to remain as participants in the longitudinal aspect of the study described in Specific Aim 2. Every week at the same time these participants will present to the CRU to collect an actigraph sleep monitor as well as sleep and pain diaries. They will then return to their homes and monitor their sleep and pain for 7 consecutive nights. Following the 7th night, they will return to the CRU to drop off their actigraph and diaries as well as provide a blood sample for the quantification of systemic inflammatory markers. Additional self-report measures of pain experiences and sleep quality will also be completed upon returning to the CRU. This protocol will be repeated 6 times across 6 consecutive weeks as described in the research strategy.

Risks to Participants

Experimental procedures. While generally safe, the experimental pain testing procedures confer some limited risks. One risk common to all procedures is that the participant will experience pain or discomfort. Specific risks of each procedure are discussed below.

1. **Heat testing procedures.** The primary hazard of the heat stimuli is minimal chance for burning of the skin. The heat may produce redness.
2. **Mechanical pressure procedures.** There is a slight chance that a bruise may form as a result of the pressure pain procedure. However, this risk is diminished by applying brief stimuli well below the participant's tolerance level.
3. **Cold pressor pain task.** There is limited risk associated with the cold pressor procedure. However, this task does produce significant increases in blood pressure in some participants. Therefore, we will exclude individuals with uncontrolled hypertension.
4. **Actigraphy.** There is some risk that the actigraph could prevent participants from sleeping comfortably. There is also minimal risk of contact dermatitis.
5. **Blood draw.** Potential risks from venipuncture include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely an infection; and, uncommonly, faintness from the procedure.
6. **Participant privacy.** Protected health information will be collected. There is always a risk that information about participants' health could be revealed inappropriately or accidentally.
7. **Discovery of HIV+ status among controls.** Controls will be tested for the presence of HIV. Although it is anticipated that controls will be HIV- per their self-report, there is potential risk that, unbeknownst to them, a control participant may test positive for HIV.

Adequacy of Protection Against Risks

Minimization of risks. The following considerations and measures will be taken to minimize potential risks to participants who consent to be involved in this study.

1. Initial screening. As part of the initial screening, participants will complete a health assessment in order to obtain information regarding their medical and health history as well as orient them to the experimental testing protocols. However, no participant will matriculate through the remainder of the study until pertinent medical and health information is reviewed and the participant is cleared by the study physician. Participants who do not meet study inclusion criteria will be dismissed from the study at this time.
2. Experimental pain testing. The experimental pain testing procedures described in this application are widely used and safe. While they produce pain, risk to the participant is minimal, because: 1) the pain is transient in nature, and generally subsides immediately after the procedure; and 2) participants are instructed that they may stop any procedure at any time with no adverse consequences. Specific protections included for each procedure are discussed below.
    A. **Heat testing procedures.** The primary hazard of heat stimulation is burning of the skin; however, burning does not occur if the temperature does not exceed 53^{o}C for a duration of 3 seconds. Precautions against skin burning include: 1) positive lockout of stimulus parameters above 51^{o}C for longer than 3 seconds; 2) participants will be informed that they can withdraw their arm from the stimulator at any time; 3) the experimenter will continuously monitor stimulus temperature and can manually discontinue stimulation at any point; and 4) the stimulator has built in shut-down system to prevent delivery of prolonged or high intensity stimuli.
    B. **Mechanical pressure procedures.** The risks of bruising and lingering pain will be diminished by applying brief stimuli well below the participant's tolerance level.
    C. **Cold pressor pain task**. The risk of excessive increases in blood pressure associated with the cold pressor procedure will be reduced by excluding individuals with uncontrolled hypertension. Also, blood pressure will be monitored throughout the procedure, and elevation in blood pressure > 180/110 will result in cessation of the procedure.
    D. **Actigraphy.** Participants will be informed that they can remove the Actiwatch at any time should it become too uncomfortable, to disruptive or sleep, or begin to produce a rash or other irritation. We do not expect this to be a major issue, as these occurrences are rare.
    E. **Blood draw.** Venipuncture will be performed under sterile conditions by appropriately trained nursing staff in the CRU. Only a small quantity of blood (approximately 10cc) will be drawn at any one time. Participants will be provided with full contact information for the research team including physician in the unlikely event that an adverse events occurs after leaving the study session.
3. Participant privacy. Several aspects of the study procedures will be designed to minimize risks to privacy by maximizing confidentiality. All paper and computer records will be identified only by a designated participant number rather than name to help ensure confidentiality. All participant records will be maintained in a locked filing cabinet inside the locked office of the PI or designees, and will be accessible only to the PI and designees. Computer data files (without participant identifiers) will be kept on computer servers with secure passwords or encrypted electronic storage devices. Consents or any other forms with identifiable participant information will be maintained in a separate file from the actual study data files.
4. Positive HIV test among control participant. In the rare event that a control participant who believes himself or herself to be HIV negative actually tests positive for HIV, this information will be disclosed to the participant. A follow up appointment with either the participant's primary care doctor or a doctor from the 1917 Clinic will be scheduled to confirm the HIV test result. If the HIV positive test result is confirmed for the control participant, he/she will be immediately connected with physical and mental health services through the UAB 1917 clinic. Counseling will also be encouraged and facilitated if desired.

Potential Benefits of the Proposed Research to Subjects and Others

The study does not establish an immediate benefit to the participant other than the financial compensation. Participants could be compensated up to $550 for completion of the entire study protocol (Aim 1 and Aim2). The potential risks of this study are small relative to the beneficial knowledge to be gleaned from conducting this research. While participants will not directly benefit from this research, it is hoped that the information gained will benefit society by providing new information regarding the impact of insomnia on pain and inflammation in PLWH

Importance of the Knowledge to be Gained

The information obtained will provide novel and important information regarding the influence of insomnia on experimental pain sensitivity and pain in everyday life, as well as inflammatory mediators of the association of sleep and pain in PLWH. Moreover, our findings will enhance the understanding of downstream consequences of insomnia on the health of PLWH. In order to reduce disparities in the burden of HIV and related comorbidities, it is important to determine the extent to which patient-level factors, including disturbed sleep (insomnia), contribute to these disparities. This will provide the foundation for more informed intervention strategies in the future, perhaps tailored to address specific issues relevant for PLWH.

Data and Safety Monitoring Plan

Because this is not a clinical trial, a formal data safety and monitoring board will not be required. In order to ensure data integrity and safety of human participants, all adverse events will be reported to both the IRB and the Center for Clinical and Translational Science for their external review. Any subsequent recommendations regarding protocol changes will be implemented. In addition, the investigators will review the reported adverse events every three months and conduct interim data analyses every 12 months to minimize the risk to the study participants.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

References

1 Roth, T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med* **3**, S7-10 (2007).
2 Schutte-Rodin, S., Broch, L., Buysse, D., Dorsey, C. & Sateia, M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med* **4**, 487-504 (2008).
3 Ohayon, M. M. Observation of the Natural Evolution of Insomnia in the American General Population Cohort. *Sleep Med Clin* **4**, 87-92, doi:10.1016/j.jsmc.2008.12.002 (2009).
4 Sateia, M. J. International classification of sleep disorders-third edition: highlights and modifications. *Chest* **146**, 1387-1394, doi:10.1378/chest.14-0970 (2014).
5 Morin, C. M., LeBlanc, M., Daley, M., Gregoire, J. P. & Merette, C. Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med* **7**, 123-130, doi:10.1016/j.sleep.2005.08.008 (2006).
6 Ohayon, M. M. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* **6**, 97-111 (2002).
7 Ohayon, M. M. & Reynolds, C. F., 3rd. Epidemiological and clinical relevance of insomnia diagnosis algorithms according to the DSM-IV and the International Classification of Sleep Disorders (ICSD). *Sleep Med* **10**, 952-960, doi:10.1016/j.sleep.2009.07.008 (2009).
8 Drake, C. L., Roehrs, T. & Roth, T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety* **18**, 163-176, doi:10.1002/da.10151 (2003).
9 Bonnet, M. H. & Arand, D. L. Consequences of insomnia. *Sleep Medicine Clinics* **1**, 351-358 (2006).
10 Vedaa, O. *et al.* Prospective study of predictors and consequences of insomnia: personality, lifestyle, mental health, and work-related stressors. *Sleep Medicine* **20**, 51-58 (2016).
11 Sofi, F. *et al.* Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol* **21**, 57-64, doi:10.1177/2047487312460020 (2014).
12 Vgontzas, A. N. *et al.* Insomnia with objective short sleep duration is associated with type 2 diabetes: A population-based study. *Diabetes Care* **32**, 1980-1985, doi:10.2337/dc09-0284 (2009).
13 Tang, N. K., Wright, K. J. & Salkovskis, P. M. Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. *J Sleep Res* **16**, 85-95, doi:10.1111/j.1365-2869.2007.00571.x (2007).
14 Woznica, A. A., Carney, C. E., Kuo, J. R. & Moss, T. G. The insomnia and suicide link: toward an enhanced understanding of this relationship. *Sleep Med Rev* **22**, 37-46, doi:10.1016/j.smrv.2014.10.004 (2015).
15 Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Lichstein, K. L. & Morin, C. M. Recommendations for a standard research assessment of insomnia. *Sleep* **29**, 1155-1173 (2006).
16 Association, A. P. *Diagnostic and statistical manual of mental disorders*. 5th edn, (American Psychiatric Publishing, 2013).
17 Reid, S. & Dwyer, J. Insomnia in HIV infection: a systematic review of prevalence, correlates, and management. *Psychosom Med* **67**, 260-269, doi:10.1097/01.psy.0000151771.46127.df (2005).
18 Gamaldo, C. E. *et al.* Sleep, function and HIV: a multi-method assessment. *AIDS Behav* **17**, 2808-2815, doi:10.1007/s10461-012-0401-0 (2013).
19 Rubinstein, M. L. & Selwyn, P. A. High prevalence of insomnia in an outpatient population with HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol* **19**, 260-265 (1998).
20 Norman, S. E. *et al.* Sleep disturbances in men with asymptomatic human immunodeficiency (HIV) infection. *Sleep* **15**, 150-155 (1992).
21 Norman, S. E., Chediak, A. D., Kiel, M. & Cohn, M. A. Sleep disturbances in HIV-infected homosexual men. *AIDS* **4**, 775-781 (1990).
22 White, J. L. *et al.* Early central nervous system response to HIV infection: sleep distortion and cognitive-motor decrements. *AIDS* **9**, 1043-1050 (1995).
23 Ferini-Strambi, L. *et al.* Slow wave sleep and cyclic alternating pattern (CAP) in HIV-infected asymptomatic men. *Sleep* **18**, 446-450 (1995).
24 Foster, S. B. *et al.* Associations of cytokines, sleep patterns, and neurocognitive function in youth with HIV infection. *Clin Immunol* **144**, 13-23, doi:10.1016/j.clim.2012.04.004 (2012).
25 Jean-Louis, G. *et al.* Insomnia symptoms and HIV infection among participants in the Women's Interagency HIV Study. *Sleep* **35**, 131-137, doi:10.5665/sleep.1602 (2012).
26 Lee, K. A. *et al.* Symptom experience in HIV-infected adults: a function of demographic and clinical characteristics. *J Pain Symptom Manage* **38**, 882-893, doi:10.1016/j.jpainsymman.2009.05.013 (2009).
27 Kenedi, C. A. & Goforth, H. W. A systematic review of the psychiatric side-effects of efavirenz. *AIDS Behav* **15**, 1803-1818, doi:10.1007/s10461-011-9939-5 (2011).

28 Omonuwa, T. S., Goforth, H. W., Preud'homme, X. & Krystal, A. D. The pharmacologic management of insomnia in patients with HIV. *J Clin Sleep Med* **5**, 251-262 (2009).

29 Cruess, D. G. *et al.* Sleep disturbance mediates the association between psychological distress and immune status among HIV-positive men and women on combination antiretroviral therapy. *J Psychosom Res* **54**, 185-189 (2003).

30 Parker, R., Stein, D. J. & Jelsma, J. Pain in people living with HIV/AIDS: a systematic review. *J Int AIDS Soc* **17**, 18719, doi:10.7448/IAS.17.1.18719 (2014).

31 Dalakas, M. C. Peripheral neuropathy and antiretroviral drugs. *J Peripher Nerv Syst* **6**, 14-20 (2001).

32 Jiao, J. M. *et al.* Chronic pain disorders in HIV primary care: clinical characteristics and association with healthcare utilization. *Pain* **157**, 931-937, doi:10.1097/j.pain.0000000000000462 (2016).

33 Merlin, J. S. *et al.* Pain and physical and psychological symptoms in ambulatory HIV patients in the current treatment era. *J Pain Symptom Manage* **43**, 638-645, doi:10.1016/j.jpainsymman.2011.04.019 (2012).

34 Miaskowski, C. *et al.* Occurrence and characteristics of chronic pain in a community-based cohort of indigent adults living with HIV infection. *J Pain* **12**, 1004-1016, doi:10.1016/j.jpain.2011.04.002 (2011).

35 Granot, M. Can we predict persistent postoperative pain by testing preoperative experimental pain? *Curr Opin Anaesthesiol* **22**, 425-430, doi:10.1097/ACO.0b013e32832a40e1 (2009).

36 Greenspan, J. D. *et al.* Pain sensitivity risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case control study. *J Pain* **12**, T61-74, doi:10.1016/j.jpain.2011.08.006 (2011).

37 Maier, C. *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. *Pain* **150**, 439-450, doi:10.1016/j.pain.2010.05.002 (2010).

38 Goodin, B. R. *et al.* Detectable Viral Load May Be Associated with Increased Pain Sensitivity in Persons Living with HIV: Preliminary Findings. *Pain Med*, doi:10.1093/pm/pnx057 (2017).

39 Smith, M. T. & Haythornthwaite, J. A. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med Rev* **8**, 119-132, doi:10.1016/S1087-0792(03)00044-3 (2004).

40 Finan, P. H., Goodin, B. R. & Smith, M. T. The association of sleep and pain: an update and a path forward. *J Pain* **14**, 1539-1552, doi:10.1016/j.jpain.2013.08.007 (2013).

41 Chung, K. F. & Tso, K. C. Relationship between insomnia and pain in major depressive disorder: A sleep diary and actigraphy study. *Sleep Med* **11**, 752-758, doi:10.1016/j.sleep.2009.09.005 (2010).

42 Nitter, A. K., Pripp, A. H. & Forseth. Are sleep problems and non-specific health complaints risk factors for chronic pain? A prospective population-based study with 17 year follow-up. . *Scandanavian Journal of Pain* **3**, 210-217 (2012).

43 Odegard, S. S. *et al.* The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). *Headache* **51**, 570-580, doi:10.1111/j.1526-4610.2011.01859.x (2011).

44 Lewandowski, A. S., Palermo, T. M., De la Motte, S. & Fu, R. Temporal daily associations between pain and sleep in adolescents with chronic pain versus healthy adolescents. *Pain* **151**, 220-225, doi:10.1016/j.pain.2010.07.016 (2010).

45 Quartana, P. J., Wickwire, E. M., Klick, B., Grace, E. & Smith, M. T. Naturalistic changes in insomnia symptoms and pain in temporomandibular joint disorder: a cross-lagged panel analysis. *Pain* **149**, 325-331, doi:10.1016/j.pain.2010.02.029 (2010).

46 Smith, M. T. *et al.* Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. *Pain* **138**, 497-506, doi:10.1016/j.pain.2008.01.028 (2008).

47 Tang, N. K., Goodchild, C. E., Sanborn, A. N., Howard, J. & Salkovskis, P. M. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. *Sleep* **35**, 675-687A, doi:10.5665/sleep.1830 (2012).

48 Haack, M. *et al.* Pain sensitivity and modulation in primary insomnia. *Eur J Pain* **16**, 522-533, doi:10.1016/j.ejpain.2011.07.007 (2012).

49 Schrimpf, M. *et al.* The effect of sleep deprivation on pain perception in healthy subjects: a meta-analysis. *Sleep Med* **16**, 1313-1320, doi:10.1016/j.sleep.2015.07.022 (2015).

50 Sivertsen, B. *et al.* Sleep and pain sensitivity in adults. *Pain* **156**, 1433-1439, doi:10.1097/j.pain.0000000000000131 (2015).

51 Chiu, Y. H. *et al.* Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. *Pain* **115**, 316-321, doi:10.1016/j.pain.2005.03.009 (2005).

52 Crum-Cianflone, N. F. *et al.* Prevalence and factors associated with sleep disturbances among early-treated HIV-infected persons. *Clin Infect Dis* **54**, 1485-1494, doi:10.1093/cid/cis192 (2012).

53 Aouizerat, B. E. *et al.* Risk factors and symptoms associated with pain in HIV-infected adults. *J Assoc Nurses AIDS Care* **21**, 125-133, doi:10.1016/j.jana.2009.10.003 (2010).

54 Vosvick, M. *et al.* Sleep disturbances among HIV-positive adults: the role of pain, stress, and social support. *J Psychosom Res* **57**, 459-463, doi:10.1016/j.jpsychores.2004.03.003 (2004).

55 Irwin, M. R. *et al.* Sleep loss activates cellular inflammatory signaling. *Biol Psychiatry* **64**, 538-540, doi:10.1016/j.biopsych.2008.05.004 (2008).

56 Mullington, J. M., Hinze-Selch, D. & Pollmacher, T. Mediators of inflammation and their interaction with sleep: relevance for chronic fatigue syndrome and related conditions. *Ann N Y Acad Sci* **933**, 201-210 (2001).

57 Solarz, D. E., Mullington, J. M. & Meier-Ewert, H. K. Sleep, inflammation and cardiovascular disease. *Front Biosci (Elite Ed)* **4**, 2490-2501 (2012).

58 Mullington, J. M., Simpson, N. S., Meier-Ewert, H. K. & Haack, M. Sleep loss and inflammation. *Best Pract Res Clin Endocrinol Metab* **24**, 775-784, doi:10.1016/j.beem.2010.08.014 (2010).

59 Motivala, S. J. Sleep and inflammation: psychoneuroimmunology in the context of cardiovascular disease. *Ann Behav Med* **42**, 141-152, doi:10.1007/s12160-011-9280-2 (2011).

60 Patel, S. R. *et al.* Sleep duration and biomarkers of inflammation. *Sleep* **32**, 200-204 (2009).

61 Zhang, J. M. & An, J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin* **45**, 27-37, doi:10.1097/AIA.0b013e318034194e (2007).

62 Ferrucci, L. *et al.* Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* **47**, 639-646 (1999).

63 Penninx, B. W. *et al.* Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc* **52**, 1105-1113, doi:10.1111/j.1532-5415.2004.52308.x (2004).

64 Meier-Ewert, H. K. *et al.* Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol* **43**, 678-683, doi:10.1016/j.jacc.2003.07.050 (2004).

65 Vgontzas, A. N. *et al.* Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab* **89**, 2119-2126, doi:10.1210/jc.2003-031562 (2004).

66 Haack, M., Sanchez, E. & Mullington, J. M. Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers. *Sleep* **30**, 1145-1152 (2007).

67 Smith, M. T., Edwards, R. R., McCann, U. D. & Haythornthwaite, J. A. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. *Sleep* **30**, 494-505 (2007).

68 Blumenthal, R., Durell, S. & Viard, M. HIV entry and envelope glycoprotein-mediated fusion. *J Biol Chem* **287**, 40841-40849, doi:10.1074/jbc.R112.406272 (2012).

69 Wilen, C. B., Tilton, J. C. & Doms, R. W. HIV: cell binding and entry. *Cold Spring Harb Perspect Med* **2**, doi:10.1101/cshperspect.a006866 (2012).

70 Holguin, A. *et al.* HIV-1 gp120 stimulates proinflammatory cytokine-mediated pain facilitation via activation of nitric oxide synthase-I (nNOS). *Pain* **110**, 517-530, doi:10.1016/j.pain.2004.02.018 (2004).

71 Milligan, E. D. *et al.* Thermal hyperalgesia and mechanical allodynia produced by intrathecal administration of the human immunodeficiency virus-1 (HIV-1) envelope glycoprotein, gp120. *Brain Res* **861**, 105-116 (2000).

72 Milligan, E. D. *et al.* Intrathecal HIV-1 envelope glycoprotein gp120 induces enhanced pain states mediated by spinal cord proinflammatory cytokines. *J Neurosci* **21**, 2808-2819 (2001).

73 Schoeniger-Skinner, D. K. *et al.* Interleukin-6 mediates low-threshold mechanical allodynia induced by intrathecal HIV-1 envelope glycoprotein gp120. *Brain Behav Immun* **21**, 660-667, doi:10.1016/j.bbi.2006.10.010 (2007).

74 Gemma, C. & Opp, M. R. Human immunodeficiency virus glycoproteins 160 and 41 alter sleep and brain temperature of rats. *J Neuroimmunol* **97**, 94-101 (1999).

75 Opp, M. R. *et al.* Human immunodeficiency virus envelope glycoprotein 120 alters sleep and induces cytokine mRNA expression in rats [published errata appear in Am J Physiol 1996 Aug;271(2 Pt 2):section R following table of contents and 1996 Dec;271(6 Pt 3):section R following table of contents]. *Am J Physiol* **270**, R963-970 (1996).

76 Sanchez-Alavez, M. *et al.* HIV- and FIV-derived gp120 alter spatial memory, LTP, and sleep in rats. *Neurobiol Dis* **7**, 384-394, doi:10.1006/nbdi.2000.0302 (2000).

77 Yuan, S. B. *et al.* Gp120 in the pathogenesis of human immunodeficiency virus-associated pain. *Ann Neurol* **75**, 837-850, doi:10.1002/ana.24139 (2014).

78 Appay, V. & Sauce, D. Immune activation and inflammation in HIV-1 infection: causes and consequences. *J Pathol* **214**, 231-241, doi:10.1002/path.2276 (2008).

79 Deeks, S. G. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* **62**, 141-155, doi:10.1146/annurev-med-042909-093756 (2011).

80 da Silva, J. G. *et al.* Level of pain and quality of life of people living with HIV/AIDS pain and quality of life in HIV/AIDS. *AIDS Care* **29**, 1041-1048, doi:10.1080/09540121.2016.1274013 (2017).

81 Finan, P. H. & Smith, M. T. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. *Sleep Med Rev* **17**, 173-183, doi:10.1016/j.smrv.2012.03.003 (2013).

82 Maes, M. *et al.* The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine* **10**, 313-318 (1998).

83 Taylor, D. J., Lichstein, K. L., Durrence, H. H., Reidel, B. W. & Bush, A. J. Epidemiology of insomnia, depression, and anxiety. *Sleep* **28**, 1457-1464 (2005).

84 Toker, S., Shirom, A., Shapira, I., Berliner, S. & Melamed, S. The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *J Occup Health Psychol* **10**, 344-362, doi:10.1037/1076-8998.10.4.344 (2005).

85 Wilson, K. G., Eriksson, M. Y., D'Eon, J. L., Mikail, S. F. & Emery, P. C. Major depression and insomnia in chronic pain. *Clin J Pain* **18**, 77-83 (2002).

86 Coates, T. J. *et al.* Estimating sleep parameters: a multitrait--multimethod analysis. *J Consult Clin Psychol* **50**, 345-352 (1982).

87 Landry, G. J., Best, J. R. & Liu-Ambrose, T. Measuring sleep quality in older adults: a comparison using subjective and objective methods. *Front Aging Neurosci* **7**, 166, doi:10.3389/fnagi.2015.00166 (2015).

88 Taibi, D. M., Price, C. & Voss, J. A pilot study of sleep quality and rest-activity patterns in persons living with HIV. *J Assoc Nurses AIDS Care* **24**, 411-421, doi:10.1016/j.jana.2012.08.001 (2013).

89 Lee, K. A., Portillo, C. J. & Miramontes, H. The influence of sleep and activity patterns on fatigue in women with HIV/AIDS. *J Assoc Nurses AIDS Care* **12 Suppl**, 19-27 (2001).

90 Ancoli-Israel, S. *et al.* The role of actigraphy in the study of sleep and circadian rhythms. *Sleep* **26**, 342-392 (2003).

91 Morgenthaler, T. *et al.* Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep* **30**, 519-529 (2007).

92 Sadeh, A. & Acebo, C. The role of actigraphy in sleep medicine. *Sleep Med Rev* **6**, 113-124 (2002).

93 Jean-Louis, G., Kripke, D. F., Cole, R. J., Assmus, J. D. & Langer, R. D. Sleep detection with an accelerometer actigraph: comparisons with polysomnography. *Physiol Behav* **72**, 21-28 (2001).

94 Lichstein, K. L. *et al.* Actigraphy validation with insomnia. *Sleep* **29**, 232-239 (2006).

95 Eisenberg, E., Midbari, A., Haddad, M. & Pud, D. Predicting the analgesic effect to oxycodone by 'static' and 'dynamic' quantitative sensory testing in healthy subjects. *Pain* **151**, 104-109, doi:10.1016/j.pain.2010.06.025 (2010).

96 Olesen, S. S., van Goor, H., Bouwense, S. A., Wilder-Smith, O. H. & Drewes, A. M. Reliability of static and dynamic quantitative sensory testing in patients with painful chronic pancreatitis. *Reg Anesth Pain Med* **37**, 530-536, doi:10.1097/AAP.0b013e3182632c40 (2012).

97 Rolke, R. *et al.* Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain* **123**, 231-243, doi:10.1016/j.pain.2006.01.041 (2006).

98 Rolke, R. *et al.* Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain* **10**, 77-88, doi:10.1016/j.ejpain.2005.02.003 (2006).

99 Arendt-Nielsen, L. & Yarnitsky, D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. *J Pain* **10**, 556-572, doi:10.1016/j.jpain.2009.02.002 (2009).

100 Backonja, M. M. *et al.* Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. *Pain* **154**, 1807-1819, doi:10.1016/j.pain.2013.05.047 (2013).

101 Merlin, J. S. *et al.* Brief Report: IL-1beta Levels Are Associated With Chronic Multisite Pain in People Living With HIV. *J Acquir Immune Defic Syndr* **75**, e99-e103, doi:10.1097/QAI.0000000000001377 (2017).

102 Morin, C. M., Belleville, G., Belanger, L. & Ivers, H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* **34**, 601-608 (2011).

103 Merikangas, K. R. *et al.* The structured diagnostic interview for sleep patterns and disorders: rationale and initial evaluation. *Sleep Med* **15**, 530-535, doi:10.1016/j.sleep.2013.10.011 (2014).

104 Bastien, C. H., Vallieres, A. & Morin, C. M. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* **2**, 297-307 (2001).

105 Erman, M. K., Stewart, D., Einhorn, D., Gordon, N. & Casal, E. Validation of the ApneaLink for the screening of sleep apnea: a novel and simple single-channel recording device. *J Clin Sleep Med* **3**, 387-392 (2007).

106 Gironda, R. J., Lloyd, J., Clark, M. E. & Walker, R. L. Preliminary evaluation of reliability and criterion validity of Actiwatch-Score. *Journal of rehabilitation research and development* **44**, 223-230 (2007).

107 Wood, A. C., Kuntsi, J., Asherson, P. & Saudino, K. J. Actigraph data are reliable, with functional reliability increasing with aggregation. *Behavior research methods* **40**, 873-878 (2008).

108 Sadeh, A. The role and validity of actigraphy in sleep medicine: an update. *Sleep Med Rev* **15**, 259-267, doi:10.1016/j.smrv.2010.10.001 (2011).

109 Sanchez-Ortuno, M. M., Edinger, J. D., Means, M. K. & Almirall, D. Home is where sleep is: an ecological approach to test the validity of actigraphy for the assessment of insomnia. *J Clin Sleep Med* **6**, 21-29 (2010).

110 Berger, A. M. *et al.* Methodological challenges when using actigraphy in research. *J Pain Symptom Manage* **36**, 191-199, doi:10.1016/j.jpainsymman.2007.10.008 (2008).

111 Carney, C. E. *et al.* The consensus sleep diary: standardizing prospective sleep self-monitoring. *Sleep* **35**, 287-302, doi:10.5665/sleep.1642 (2012).

112 Vgontzas, A. N. *et al.* IL-6 and its circadian secretion in humans. *Neuroimmunomodulation* **12**, 131-140, doi:10.1159/000084844 (2005).

113 Amtmann, D. *et al.* Development of a PROMIS item bank to measure pain interference. *Pain* **150**, 173-182, doi:10.1016/j.pain.2010.04.025 (2010).

114 Cella, D. *et al.* The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *Journal of clinical epidemiology* **63**, 1179-1194, doi:10.1016/j.jclinepi.2010.04.011 (2010).

115 Revicki, D. A. *et al.* Development and psychometric analysis of the PROMIS pain behavior item bank. *Pain* **146**, 158-169, doi:10.1016/j.pain.2009.07.029 (2009).

116 Lewinsohn, P. M., Seeley, J. R., Roberts, R. E. & Allen, N. B. Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging* **12**, 277-287 (1997).

117 Marteau, T. M. & Bekker, H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *Br J Clin Psychol* **31 (Pt 3)**, 301-306 (1992).

118 Bulls, H. W. *et al.* Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. *J Pain Res* **8**, 311-320, doi:10.2147/JPR.S84607 (2015).

119 Goodin, B. R. *et al.* Salivary cortisol and soluble tumor necrosis factor-alpha receptor II responses to multiple experimental modalities of acute pain. *Psychophysiology* **49**, 118-127, doi:10.1111/j.1469-8986.2011.01280.x (2012).

120 Cruz-Almeida, Y. & Fillingim, R. B. Can quantitative sensory testing move us closer to mechanism-based pain management? *Pain medicine* **15**, 61-72, doi:10.1111/pme.12230 (2014).

121 Yarnitsky, D. *et al.* Recommendations on practice of conditioned pain modulation (CPM) testing. *Eur J Pain* **19**, 805-806, doi:10.1002/ejp.605 (2015).

122 Staud, R., Vierck, C. J., Cannon, R. L., Mauderli, A. P. & Price, D. D. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* **91**, 165-175 (2001).

123 Cruz-Almeida, Y. *et al.* Age differences in cytokine expression under conditions of health using experimental pain models. *Exp Gerontol* **72**, 150-156, doi:10.1016/j.exger.2015.09.017 (2015).

124 Dabitao, D., Margolick, J. B., Lopez, J. & Bream, J. H. Multiplex measurement of proinflammatory cytokines in human serum: comparison of the Meso Scale Discovery electrochemiluminescence assay and the Cytometric Bead Array. *J Immunol Methods* **372**, 71-77, doi:10.1016/j.jim.2011.06.033 (2011).

125 McKay, H. S. *et al.* Multiplex assay reliability and long-term intra-individual variation of serologic inflammatory biomarkers. *Cytokine* **90**, 185-192, doi:10.1016/j.cyto.2016.09.018 (2017).

126 Morin, C. M. *et al.* Monthly fluctuations of insomnia symptoms in a population-based sample. *Sleep* **37**, 319-326, doi:10.5665/sleep.3406 (2014).

127 Pillai, V., Roth, T. & Drake, C. L. The nature of stable insomnia phenotypes. *Sleep* **38**, 127-138, doi:10.5665/sleep.4338 (2015).
128 Melzack, R. The short-form McGill Pain Questionnaire. *Pain* **30**, 191-197 (1987).
129 Diggle, P. J., Heagerty, P., Liang, K.-Y. & Zeger, S. L. *Analysis of longitudinal data*. 2nd edn, (Oxford University Press, 2002).

Scope of Work

NIH Project Title: The impact of insomnia on pain, physical function, and inflammation in HIV

Subaward PI: Dr. Jessica Merlin, MD, PhD, University of Pittsburgh

Period of Performance: 9/1/2018 – 8/31/2023

Document Date: 4/7/18

Project Background and Need for Subaward: The overall objective of this application is to investigate the impact of insomnia on pain, physical functioning, and inflammation in persons living with HIV (PLWH). Our central hypothesis is that insomnia promotes pain symptoms and sensitivity, poor physical functioning, as well as systemic and pain-evoked inflammation in PLWH. The study requires the expertise of someone with background in HIV research and clinical care. As a physician scientist, this is exactly what I bring to this this project.

Subrecipient's Scope of Work: I have developed expertise in HIV and chronic pain over the past 10 years, beginning with my infectious diseases and palliative care fellowships. I am one of three people in the US fellowship trained in both of these disciplines. I began working on HIV and chronic pain as an infectious diseases fellow, and published my first paper on this topic in 2011. My research in this area has included the clinical epidemiology of chronic pain in individuals with HIV in the Center for AIDS Research Network of Integrated Clinical Systems Database, psychometric work on a new Brief Chronic Pain Questionnaire used to identify chronic pain in individuals with HIV, and qualitative work on the chronic pain experience in this population. Responsibilities for this application will include assisting the PI (Goodin) with all aspects of study conceptualization and design. I will assist and advise with recruitment, the medical evaluation of participants via electronic medical records, assessment of health history and medical comorbidities. This will all be done to determine appropriateness of patients for continued matriculation through the study protocols.

Reporting Schedule: I will make quarterly visits to UAB in order to fulfill my responsibilities, in addition to being involved in regular conference calls and study team meetings.

Deliverables: The study will be conducted in its entirety at UAB. For this reason, only salary support (10% yearly effort) is being budgeted for my time and contributions to this project. Dr. Goodin and I have an established record of productive research collaboration together. He can expect more of the same for the purpose of this project. In addition to providing my expertise to study conceptualization and design efforts, I will also assist with all aspects of data interpretation, manuscript writing, and scholarly presentations.

Payment Schedule: Not applicable. There will be no charges or invoices submitted to the University of Pittsburgh.

UAB CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

Knowledge that will change your world

March 1, 2018

Burel Goodin, PhD
UAB Departments of Psychology and Anesthesiology
Campbell Hall, Room 328
1300 University Blvd.
Birmingham, AL 35294-1170

Dear Burel,

I am writing to indicate my support for your upcoming CNIHF proposal, "The impact of insomnia on pain, physical function, and inflammation in HIV." As Director of UAB's NIH-funded Clinical Research Unit (CRU), I can assure you that the Center for Clinical and Translational Science (CCTS) will provide clinical services support for your project. Specifically, we can provide the following services:

Blood draws: Outpatient facilities are available for performing blood draws. The CRU nursing staff is available from 7am – 5pm Monday through Friday to draw blood specimens.

Sample processing: The CRU processing laboratory can centrifuge, separate, aliquot, and store specimens that are generated from the blood draws.

Patient rooms: Our facilities have adequate space for collection of clinical, biomarker, psychosocial, QST, and functional performance data.

The infra-structure of the CCTS (UAB's Clinical and Translational Science Award) will provide assistance with clinical and laboratory needs for your study. If there are any additional ways the CCTS can be of assistance, please let me know. I wish you the best of luck with your proposal.

Sincerely,

J. B. Nabors

Burt Nabors, MD
Director, Clinical Research Unit
UAB Center for Clinical and Translational Science

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Department of Nutrition Sciences
Barbara A. Gower, PhD, Professor
Webb 616A, 1675 University Blvd; 35294-3360
bgower@uab.edu; 205-934-4087

April 2, 2018

Burel R. Goodin, Ph.D.
Associate Professor
Departments of Psychology and Anesthesiology
University of Alabama at Birmingham
Campbell Hall, Room 328
1300 University Blvd.
Birmingham, AL 35294

Dear Dr. Goodin:

I am pleased to provide a letter of support for your R01 application entitled “The impact of insomnia on pain, physical function, and inflammation in HIV.” Based upon my previous discussions with you, I understand that you will be examining a large panel of pro- and anti-inflammatory cytokines as well as several other acute-phase markers of inflammation to determine whether these biomarkers are important for helping to explain how insomnia drives the pain experiences and physical functioning of persons living with HIV. Insomnia and pain are both appear to be important health comorbidities that commonly affect persons living with HIV; however, this topic has only received minimal empirical attention to date. Furthermore, little is known about the role that inflammation might play in linking insomnia with pain and poor physical function. Thus, I am confident that your project will provide much useful data to advance the field in this area.

As director of the UAB DRC/CCTS Human Physiology and Metabolism Cores, I have extensive experience in the analysis of vitamins, hormones, and inflammatory factors. My staff and I are happy to assist you in the quantification of cytokines and other inflammatory markers using immunoassay as part of the Meso Scale Discovery platform. As such we are equipped to assay pro-inflammatory (TNF-α, IL1-β, IL-6, IL-12, IL-18, C-reactive protein, sCD14/163, D-dimer, and IFN-gamma), as well as anti-inflammatory (IFN-alpha, TGF-beta, IL4, IL-10, and IL-13) markers. We do not anticipate any difficulties in achieving reproducible and highly accurate analytical determinations of these biomarkers in your samples.

I wish you good luck with your application, and I look forward to working with you.

Sincerely,

Barbara Gower, Ph.D.
Professor and Vice-Chair for Research, Department of Nutrition Sciences
Director, NORC/CCTS Metabolism Core; DRC Human Physiology Core
University of Alabama at Birmingham

April 18, 2018

Burel R. Goodin, Ph.D.
Associate Professor
Departments of Psychology and Anesthesiology
University of Alabama at Birmingham
Campbell Hall, Room 328
1300 University Blvd.
Birmingham, AL 35294

Dear Dr. Goodin:

The purpose of this letter is to affirm my strong support of your R01 application: "**The impact of insomnia on pain, physical function, and inflammation in HIV**." We will be pleased for you to recruit patient participants from the UAB 1917 Clinic (Est. 1988). There are currently 3,300 adult patients living with HIV from our 7-county service area (Blount, Cullman, Jefferson, Shelby, St. Clair, Walker & Winston) and beyond who receive comprehensive care at the 1917 Clinic. Insomnia and pain are some of their common complaints. I am confident that you will enroll the necessary number of participants for your study.

For 30 years the UAB 1917 Clinic has provided comprehensive medical and social services to patients living with HIV. Medical specialty, dental and mental health services are available onsite. We receive Ryan White HIV/AIDS Treatment Modernization Act funding to provide comprehensive care for low-income, uninsured and under-insured adults with HIV regardless of any pre-existing or non-HIV related conditions. Patients are not denied service based on inability to pay copays, sliding scale fees or other payments.

I am fully committed to provide support to ensure the success of the proposed research. In addition to the privilege of recruiting patients at the 1917 Clinic, you will have access to UAB 1917 Clinic facilities and resources. We look forward to working with you on this important research project and trust that your application will receive a favorable scientific review.

Sincerely,

Jim Raper, PhD, CRNP, JD
Director, 1917 Clinic
Professor of Medicine and Nursing
Equity Advisor
University of Alabama at Birmingham
908 20th Street So
CCB-245
Birmingham, AL 35249-2050
jlraper@uabmc.edu

CENTER FOR AIDS RESEARCH
Department of Medicine, Division of Infectious Diseases
Michael S. Saag, MD

March 29, 2018

Burel R. Goodin, Ph.D.
Associate Professor
Departments of Psychology and Anesthesiology
University of Alabama at Birmingham
Campbell Hall, Room 328
1300 University Blvd.
Birmingham, AL 35294

Dear Dr. Goodin:

As you know, I am currently the Director of the UAB Center for AIDS Research (CFAR), Associate Dean for Global Health in the School of Medicine, and Professor of Medicine in the Division of Infectious Diseases. As such, I am currently well positioned to support your research efforts related to your R01 application titled, “The impact of insomnia on pain, physical function, and inflammation in HIV." I have been very impressed with the progression of your CFAR-sponsored pilot award (Creative and Novel Ideas in HIV Research; CNIHR) and the preliminary data you have generated for the purpose of the current proposal. I am confident that this R01, should it be funded, would generate high quality and informative data that will be relevant for researchers and clinicians alike.

The UAB CFAR offers access to core facilities that support and promote multidisciplinary HIV/AIDS research efforts. For example, our Clinical Core may be particularly relevant to your study needs. This is because the Clinical Core provides easy access to comprehensive clinical services, as well as resources and expertise supporting basic science, behavioral, epidemiological, translational, clinical, and public health research. Clinical Research Training Services are provided at all levels including the 1917 Clinic Cohort, which is an opportunity for investigators from across campus to meet to discuss HIV research. The Clinical Core is rapidly adapting and instituting innovative and expanded services in response to user needs and to support the overarching UAB CFAR scientific mission. You will have access to all CFAR core facilities as needed for the conduct of your study.

I am enthusiastic about this proposal. I believe that your focus on HIV-related comorbidities including insomnia and pain, as well as the investigators involved with this study, will contribute important insights to study outcomes. Overall, I believe this line of work will help to improve our understanding of the consequences of insomnia for people living with HIV and make impactful scientific contributions that advance the field.

I wish you the best of luck regarding the scientific review of this very important research project.

Sincerely,

Michael S. Saag, M.D.
Professor of Medicine
Director, UAB Center for AIDS Research, Jim Straley Chair in AIDS Research
National PI, CFAR Network of Integrated Clinical Systems-CNICS
Phone: 205-934-7349
Email: msaag@uabmc.edu

Resource Sharing Plan

The resources generated under the auspices of this project are expected to represent substantial value to the scientific community. Therefore, we propose the following resource sharing plan. We will maintain full control over the data and resources for a period of 1 year following completion of data collection. This will allow sufficient time for data cleaning, validation and analysis, and subsequent publication of the primary findings that address the proposed specific aims of the project. After this time, de-identified datasets with full data dictionaries, including data from biomarker assays, will be made publicly available through the National Institutes of Health. Before the data become publicly available, individual requests for data sharing will be considered by the Principal Investigators, Co-Investigators, and the NIH staff on a case-by-case basis. Evaluation of these requests will be based on the scientific validity of the proposal as well as the adequacy of plans for maintaining security and confidentiality of the data. The Data and Clinical Coordinating Center at the University of Alabama at Birmingham will assist in the implementation of the resource sharing plan.

Authentication of Key Resources Plan

The study outlined in the attached proposal is designed in such a fashion as to assure that the resulting data are replicable through the use of rigorous methodological controls and attention to key biological and chemical resources as noted below:

Biological Resources

No biologicals or cell lines are to be utilized as part of this study.

Chemical Resources

Antibodies: Per discussions with study contributors (Dr. Barbara Gower), all antibodies used in immunoassays for inflammatory cytokines and other proteins (TNF-α, IL1-β, IL-6, IL-12, IL-18, C-reactive protein, sCD14/163, D-dimer, and IFN-gamma, IFN-alpha, TGF-beta, IL4, IL-10, and IL-13) will be purchased from commercial suppliers such as Meso Scale Discovery and Cayman Chemical, respectively. In each case, following successful immunohistological labeling, the lot numbers will be noted and requested for all future orders. In the event that a specific lot is no longer available, the new batch of antibody will be tested against the old lot and antibody dilutions determined. In all publications and presentations the lot number and supplier of the antibodies will be reported.

Other

Actigraphy: Objective sleep measurements will be made using a wrist-worn actigraph purchased through a commercial vendor, Philips Respironics. The specific actigraph model referred to as the Actiwatch2 will be used exclusively in this study. In all publications and presentations we will make reference to Philips Respironics and Actiwatch2 when addressing objective sleep data.
http://www.actigraphy.com/solutions/actiwatch/actiwatch2.html

Home Sleep Testing: ResMed's ApneaLink Air™ home sleep testing system will be purchased and utilized for this study to assess for obstructive sleep apnea. This system provides a reliable and validated means of monitoring for obstructive sleep apnea using a compact, lightweight and easy-to-use home sleep testing device. A cost-efficient, type III home sleep testing device, the ApneaLink Air is capable of recording up to five channels of information: respiratory effort, pulse, oxygen saturation, nasal flow and snoring. In all publications and presentations we will make reference to ResMed's ApneaLink Air™ when addressing obstructive sleep apnea.
http://www.resmed.com/us/en/healthcare-professional/products/diagnostics/apnealink-air.html#Support

Experimental Pain Testing: All necessary equipment has already been purchased from the PI's existing resources. This will allow for complete and comprehensive assessment of experimental pain sensitivity. Commercial vendors that provide this equipment include Medoc (Pathway Thermal Sensory Analyzer, Algomed Algometry System) and Thermo Scientific (cold pressor). We have experience with attainment, use, and maintenance of this equipment, and we are confident in the reproducibility of the data produced. All equipment is publicly available for purchase. We will be transparent about how this equipment was used, and the data obtained, when reporting for publications and presentations.

Study Questionnaires: All study questionnaires are freely available measures that can be found on the internet with simple search engine utilization. For instance, NIH PROMIS measures can be requested by visiting the following website: http://www.nihpromis.org/default. All study measures are reliable and valid assessments of their given content domains. This will maximize the likelihood of obtaining rigorous and reproducible data that can be widely disseminated. Information pertaining to each study questionnaire will be made available to other researchers either by request or through publication and presentation.

SUMMARY STATEMENT

PROGRAM CONTACT:
Elisabet Caler
301-435-0222
lis.caler@nih.gov

(Privileged Communication)

Release Date: **11/28/2018**
Revised Date:

Application Number: **1 R01 HL147603-01**

Principal Investigator

GOODIN, BUREL R.

Applicant Organization: UNIVERSITY OF ALABAMA AT BIRMINGHAM

Review Group: **HCCS**
HIV Comorbidities and Clinical Studies Study Section
AIDS

Meeting Date: **11/14/2018**
Council: **JAN 2019**
Requested Start: **04/01/2019**

RFA/PA: **PA18-484**
PCC: **LLLD A**
Dual IC(s): **AI**

Project Title: **The Impact of Insomnia on Pain, Physical Function, and Inflammation in HIV**

SRG Action: **Impact Score:39 Percentile:19**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **30-Human subjects involved - Certified, no SRG concerns**
Animal Subjects: **10-No live vertebrate animals involved for competing appl.**
Gender: **1A-Both genders, scientifically acceptable**
Minority: **1A-Minorities and non-minorities, scientifically acceptable**
Children: **1A-Both Children and Adults, scientifically acceptable**

Project Year	Direct Costs Requested	Estimated Total Cost
1	450,916	658,557
2	452,871	661,412
3	459,925	671,715
4	472,330	689,832
5	464,661	678,631
TOTAL	2,300,703	3,360,147

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01HL147603-01 Goodin, Burel

RESUME AND SUMMARY OF DISCUSSION: In this application the Principal Investigator examines the effects of insomnia on pain sensitivity and overall systemic inflammation in persons living with HIV (PLWH). Prevalence of insomnia is higher among HIV infected populations as well as the development of chronic pain. Based on previous studies and the team's preliminary data, insomnia among HIV infected populations was associated with increased pain sensitivity and greater reactivity of inflammatory cytokines. The PI proposes to expand upon these observations by looking more in depth at the effects of insomnia as well as the role weekly fluctuations play in the development of pain. The reviewers agreed that this is a well-written application with high significance as it addresses an area of study in chronic HIV that is underappreciated. The studies were considered both technically and conceptually innovative as they employ a number of measurements to study the influence of sleep on pain. Major strengths include the solid preliminary data, the strong investigative team, the rigorous as well as feasible experimental approaches. Enthusiasm for the application was dampened by the limited appreciation for confounding comorbidities including mental health and the large amount of longitudinal data to be generated. Moreover, the reviewers agreed that the rather burdensome measures of pain and blood draws for inflammatory markers may impact the study's feasibility. Overall, the panel agreed that this is a well written application from a strong investigative team exploring an understudied disorder impacting PLWH. However, the weaknesses identified mainly in the approach lowered overall enthusiasm to moderately high.

DESCRIPTION (provided by applicant): Insomnia is a sleep disorder characterized by difficulty falling asleep, staying asleep, or both, despite adequate opportunity for sleep attainment. As a result, people with insomnia may get too little sleep and/or have poor sleep quality. Insomnia is a common and debilitating sleep disorder in persons living with HIV (PLWH), with prevalence estimates ranging from 30-73%. Insomnia is increasingly viewed as a risk factor for the onset and/or worsening of pain symptoms and physical functioning deficits. Insomnia has been found to promote enhanced pain sensitivity (also known as hyperalgesia), which is critical to the etiology of pain in everyday life. This is particularly relevant for PLWH because recent evidence attests to the fact that pain symptoms are quite prevalent in the daily lives of PLWH. Whether insomnia is a risk factor for the experience of pain and poor physical functioning in PLWH is a topic that has received minimal attention to date; therefore, additional research is needed. Inflammatory processes represent an important biologic mechanism linking insomnia to pain and physical function. Insomnia promotes systemic inflammation as well as inflammatory reactivity to physical stressors like pain. Research conducted with non-HIV samples has shown that inflammation can substantially increase sensitivity to painful stimuli in the laboratory setting, as well as exacerbate pain symptoms in everyday life and physical disability. Taken together, insomnia may drive pain and physical function in PLWH through the proliferation of inflammatory mediators. There is currently a need to elucidate mechanisms and mediators of sleep disorders in PLWH, and the consequences and influences of these disturbances on other HIV-related comorbidities. Accordingly, the overall objective of this proposal is to investigate the impact of insomnia on pain, physical function, and inflammation in PLWH. We will accomplish our overall objective by addressing the following specific aims: 1) determine whether insomnia promotes increased experimental pain sensitivity and exaggerated inflammatory reactivity to painful stimuli in PLWH, and 2) determine if fluctuations in insomnia burden over time drive inflammation and pain in everyday life, and physical functioning among PLWH. These aims will be addressed using study methods developed and rigorously refined by our research team, and which have previously yielded promising preliminary results suggesting that insomnia may indeed promote pain and inflammation in PLWH. This approach is innovative because the impact of insomnia on pain and pain-related inflammatory processes has never before been directly examined in PLWH. Furthermore, the incorporation of objective as well as subjective measures of sleep and physical function, experimental pain testing, and a wide array of pro- and anti-inflammatory biomarkers also contributes to the innovation of this proposal. The proposed research will be significant because, if our hypotheses are confirmed, we will identify: 1) insomnia as a major driver of pain and

physical functioning in the laboratory and in everyday life among PLWH, and 2) inflammation as an important insomnia-related mediator of pain in PLWH.

PUBLIC HEALTH RELEVANCE: Due to its prevalence and impact on quality of life and overall health, the Centers for Disease Control and Prevention has called insufficient sleep (i.e., insomnia) a “public health crisis.” Therefore, this proposal is relevant to public health because it seeks to elucidate the pain-related consequences of insomnia and underlying inflammatory mechanisms in accordance with the mission of the National Center on Sleep Disorders Research Plan, which states “mechanistic studies are needed to define the genomic, physiological, neurobiological, and developmental impact of sleep and circadian disturbances, and identify vulnerable populations”, such as persons living with HIV. Insomnia is an important and understudied comorbidity among persons living with HIV; therefore, this proposal is responsive to the NIH's HIV Research Priorities, which identify comorbidities as high priority research topic.

CRITIQUE 1

Significance: 5
Investigator(s): 2
Innovation: 3
Approach: 4
Environment: 1

Overall Impact: This is a well written R01 proposal from a productive PI with expertise in pain, and more recent investigations in HIV. The PI and team are proposing to address a potentially significant problem- the intersection of sleep, pain, and inflammation in PLWH. Strong preliminary data supports a rigorous and feasible approach. There are minor weaknesses in the significance and approach, but the investigative team and environment are strong, and there are innovative aspects of the proposal that drove the overall impact score.

1. Significance:

Strengths

- Truly underappreciated comorbidity
- The potential for significance/impact due both to the magnitude of persons affected, and the importance of the associated problems (pain, inflammation), and intervention
- Rigor and reproducibility are addressed and strong
- Helpful, clear, simple conceptual model
- Compelling data regarding HIV proteins and sleep/pain sensitivity

Weaknesses

- Sleep and insomnia are challenging- and likely multifactorial- variables to quantify/define
- The assertion (section A5) that “inflammation brought on by chronic insomnia increases the risk of cardiovascular disease”, etc. is overstated based on the citations provided. No connections made between sleep and outcomes in the cited references

2. Investigator(s):

Strengths

- Accomplished PI and co-Is in the needed complementary fields to accomplish the work

- Good collaboration and productivity between the PI and the ID co-I

Weaknesses

- Co-I Merlin recently re-located to a new institution and is supported by a K23
- No clinical HIV expert collaborator based at PIs institution

3. Innovation:

Strengths

- Rigorous quantification and analysis of sleep and pain sensitivity
- Home sleep testing
- Measurement techniques not often applied to PLWH- e.g. sleep actigraphs
- Both static and dynamic pain measurements

Weaknesses

- No novel biomarkers or pathways proposed

4. Approach:

Strengths

- Compelling preliminary data on pain and inflammation in PLWH
- Will be able to address direction of associations/causality (and thus, mechanisms) to some extent with aim 2 analyses.
- Combined subjective and objective data will enhance results, generalizability, and impact
- Inclusion of some simple functional measures may provide additional directions/impact
- Strong analysis/statistical plan- sufficiently detailed but still accessible by a non-statistician

Weaknesses

- Pain testing is potentially burdensome, but the PI has successfully enrolled participants to studies using the proposed techniques
- Somewhat burdensome aim 2 design/measurements; some minor concern about feasibility for this population; not clear that this depth of assessment has been performed in preliminary studies
- At least 100 aim 2 participants with daily pain and sleep diaries, and in-person assessments weekly x 6 weeks = 600 not inconsequential study visits and an immense amount of data; would like to have seen this addressed more specifically in obstacles and alternatives
- EFV use is addressed, but controlling for this in analysis may not be sufficient to address potential confounding by indication- persons with baseline disordered sleep were probably less likely to be exposed; those still on it were likely predisposed to tolerate it or maintain lower levels due to drug metabolism gene variants
- Current EFV use may be limited enough that the decision not to exclude EFV users should be re-considered
- Mood and mental health is address, but to a limited extent

5. Environment:

Strengths

- Infrastructure for clinical/translational research at 1917 Clinic is strong
- No concerns about the environment/support of the proposed work

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- No concerns

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically
- No concerns

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2

Significance: 1
Investigator(s): 2
Innovation: 2
Approach: 3

Environment: 1

Overall Impact: Insomnia in HIV infected persons is a significant public health concern affecting up to 70% of the infected population. The extent, causes and consequences of insomnia is greatly understudied. This new R01 application seeks to determine whether insomnia is a risk factor for the experience of pain through an inflammatory downstream biological consequence of chronic insomnia disorders. The proposed hypothesis to be tested is that insomnia may drive pain and physical function in PLWH through the proliferation of inflammatory mediators. The investigators are highly experienced and well suited to conduct this provocative study. There is good innovation that will use both subjective and non-subjective measure of sleep, sensitive measures of pain and physical functioning and inflammatory measures. Aim 1 proposes to determine whether insomnia promotes increased experimental pain sensitivity and exaggerated inflammatory reactivity to painful stimuli in PLWH. Aim 2 has a well- constructed approach to address how changes in insomnia are related to pain and inflammation this would be informative. Preliminary data presented by the PI support the hypothesis and are compelling showing clear relationships with insomnia and pain burden. A feasible and clear project timeline and analyses plan presented are strengths. Weaknesses include the limited information of the cohort to be studied, consideration for drug use, ART and circadian changes in the analysis plan. The depth of inflammatory measures was not as innovative and may not be as informative mediators. Despite some of these weaknesses this is a highly significant area of investigation and if the hypotheses tested are correct would be highly impactful to the field and open new avenues of research for PLWH.

1. Significance:

Strengths

- Non-neuropathic and chronic pain is common in PLWH throughout the lifetime and is a significant burden with limited studies defining mechanisms driving this co-morbidity available.
- Three preliminary pilot studies were conducted and have generate compelling results on the downstream health consequences of insomnia in PLWH, that justify the approach and capabilities of the research team to conduct the studies proposed.
- Should the study be successful this would be impactful to the field

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- The PI is an Associate Professor of Psychology and Anesthesiology at UAB with a body of research in musculoskeletal pain and disparities research and I currently R01 funded in pain related research and has an extensive publication record in pain research.
- Strong supportive letter from several senior faculty at UAB to provide clinical samples and related support.

Weaknesses

- Publications tend to be targeted to specific area of research not to broader high impact journals.

3. Innovation:

Strengths

- This is one of the few studies proposing to directly examine the interrelationship between insomnia, inflammation, pain, and physical function in PLWH which is an understudied area.
- The exploration of sleep disturbances using unique tools such as actigraphy specifically in this population is unique and will provide an improvement over current data sets assessing sleep burden.

Weaknesses

- None noted.

4. Approach:

Strengths

- A strong body of literature to justify Aim 1 and Aim 2 is presented and will provide an improvement over current data sets assessing sleep burden.
- Aim 2 is a well-designed experimental approach and cohesive and if successful will provides additional information on inflammatory mechanism over time that may impact changes in sleep patterns and burden in the study.
- A clear timeline and analyses plan is presented and previous studies by the PI have assessed gender differences *(Bulls, et al. (2015). Sex differences in experimental measures of pain sensitivity and endogenous pain inhibition. Journal of Pain Research, 8, 311.)* and this is taken into consideration but not defined in the analyses of this proposal.

Weaknesses

- The description of the cohort is rather limited with no information on ART use, type and influence this may have on the data.
- Assessment of cellular markers of immune activation is a missed opportunity.
- HIV envelope glycoproteins will be measured to explain the effects of HIV on pathology of sleep disturbances however consideration of other factors such as Nef and Tat were not considered and may play an alternate or combinatorial role in the suggested mechanism.
- The selection of inflammatory markers is rather standard, and most have been extensively assessed in PLWH and would only incrementally advance the field That said the PI has suggested alternate approaches to assess additional markers, but this is not defined insufficient detail
- The influence of Circadian changes where not considered in the research plan
- Given the use of drugs of abuse in PLWH controlling for this confounding effect was not considered in the analyses plan or recruitment criteria as this would impact data interpretation.

5. Environment:

Strengths

- University of Alabama at Birmingham (UAB) Sleep/Wake Disorders Center conducts large scale studies of insomnia and is a valuable resource for the PI to effectively carry out the proposed study.

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis:
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

Authentication of Key Biological and/or Chemical Resources:

Acceptable

Budget and Period of Support:

Budget Modifications Recommended (in amount/time)

- PI effort to reduce to 30%

CRITIQUE 3

Significance: 3
Investigator(s): 3
Innovation: 4
Approach: 5
Environment: 1

Overall Impact: This is an interesting proposal to conduct an experimental study that examines whether differential inflammation during the experience of acute pain explains greater pain sensitivity in HIV and insomnia (a full 2 x 2 intact groups design). Although these kinds of mechanistic data are needed, the possibility for important confounders (e.g., psychiatric status, chronic pain, detectable viral load) to obscure the findings is a moderate weakness. The immunologic aspects of the approach are also not sufficiently mechanistic to yield meaningful insights that will catalyze the development of new treatments for pain.

1. Significance:

Strengths

- Chronic pain is prevalent in HIV and research is needed to understand the bio-behavioral processes that contribute to pain sensitivity.

Weaknesses

- It is unclear how the experimental procedures would have clear clinical relevance or propel the development of new treatments for pain in HIV.

2. Investigator(s):

Strengths

- Strong investigative team with expertise in laboratory-based procedures for measuring pain tolerance.
- A physician scientist with expertise in pain and HIV will provide support for the clinical aspects of this application.

Weaknesses

- It is unclear whether there is sufficient expertise in immunology on the team.

3. Innovation:

Strengths

- Employs experimental pain tolerance procedures.

Weaknesses

- The focus on plasma inflammatory mediators is not innovative.

4. Approach:

Strengths

- Strong pilot data that supports feasibility of recruitment and the scientific premise.
- Experimental laboratory procedures for pain sensitivity increase scientific rigor and pilot data support differential inflammation changes in the laboratory as a function of insomnia.
- Home sleep testing will exclude participants with suspected apnea and actigraphy will provide important data on sleep between the experimental sessions.

Weaknesses

- The approach does not address prevalent psychiatric comorbidities in people living with HIV (e.g., depressive disorders, bipolar disorders) that have been shown to frequently co-occur with insomnia.
- Consider HIV-associated inflammation and how this could confound the comparison of HIV-positive persons with and without insomnia. What is the justification for enrolling HIV+ persons with a detectable HIV viral load?
- If the role of HIV in pain is well-established, what is the rationale for enrolling HIV- participants?
- Will those with chronic pain be excluded? Chronic pain one contributing factor in insomnia and prescription opioids have been shown to affect inflammation.

- The immunologic aspects of this proposal are not sufficiently mechanistic, diminishing the likelihood that viable targets for new treatments would be identified.
- Measures of cardiac reactivity (e.g., heart rate variability) and neuroendocrine responses (e.g., salivary cortisol) during the laboratory tasks would provide important information on the potential mechanistic role of the stress response. For example, the cold pressor task has a long history of being used in stress reactivity studies.

5. Environment:

Strengths

- The academic environments at UAB and U Pitt will substantially support the successful execution of this project.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Not applicable
- Inclusion/Exclusion of Children under 18: Excluding ages <18; justified scientifically

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS' WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS: ACCEPTABLE

INCLUSION OF WOMEN PLAN: ACCEPTABLE

INCLUSION OF MINORITIES PLAN: ACCEPTABLE

INCLUSION OF CHILDREN PLAN: ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 R01 HL147603-01; PI Name: Goodin, Burel R.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

HIV Comorbidities and Clinical Studies Study Section
AIDS and Related Research Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
HCCS
11/14/2018 - 11/15/2018

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

CHAIRPERSON(S)

GEIGER, JONATHAN DAVID, PHD
CHESTER FRITZ DISTINGUISHED PROFESSOR
DEPARTMENT OF BIOMEDICAL SCIENCES
SCHOOL OF MEDICINE AND HEALTH SCIENCES
UNIVERSITY OF NORTH DAKOTA
GRAND FORKS, ND 58203

MEMBERS

AKBARALI, HAMID I., PHD *
PROFESSOR AND VICE CHAIR
DEPARTMENT OF PHARMACOLOGY AND TOXICOLOGY
VIRGINIA COMMONWEALTH UNIVERSITY
RICHMOND, VA 23298

ASMUTH, DAVID M, MD *
PROFESSOR
DEPARTMENT OF INTERNAL MEDICINE
DIVISION OF INFECTIOUS DISEASES
UNIVERSITY OF CALIFORNIA DAVIS, MEDICAL CENTER
SACRAMENTO, CA 95817

BOOZE, ROSEMARIE M, PHD *
PROFESSOR AND BICENTENNIAL ENDOWED CHAIR
DEPARTMENT OF PSYCHOLOGY
UNIVERSITY OF SOUTH CAROLINA
COLUMBIA, SC 29208

BUKRINSKY, MICHAEL ILYA, MD, PHD *
PROFESSOR
DEPARTMENT OF MICROBIOLOGY, IMMUNOLOGY,
AND TROPICAL MEDICINE
SCHOOL OF MEDICINE AND HEALTH SCIENCES
GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC 20037

BURDO, TRICIA HELEN, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF NEUROSCIENCE
SCHOOL OF MEDICINE
TEMPLE UNIVERSITY
PHILADELPHIA, PA 19140

CADE, WILLIAM TODD, PHD *
PROFESSOR OF PHYSICAL THERAPY/MEDICINE
PROGRAM IN PHYSICAL THERAPY
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
ST. LOUIS, MO 63108

CARRICO, ADAM WAYNE, PHD *
ASSOCIATE PROFESSOR
DIVISION OF PREVENTION SCIENCE AND
COMMUNITY HEALTH
DEPARTMENT OF PUBLIC HEALTH SERVICES
UNIVERSITY OF MIAMI
CORAL GABLES, FL 33146

COLE, STEPHEN R, PHD
PROFESSOR
DEPARTMENT OF EPIDEMIOLOGY
GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL
CHAPEL HILL, NC 27599

DONENBERG, GERI R, PHD *
ASSOCIATE DEAN
PROFESSOR OF MEDICINE
DEPARTMENT OF PHYCHIATRY
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, IL 60608

ESTRELLA, MICHELLE M, MD *
ASSOCIATE PROFESSOR
KIDNEY HEALTH RESEARCH COLLABORATIVE
DEPARTMENT OF MEDICINE
UNIVERSITY OF CALIFORNIA
SAN FRANCISCO AND SAN FRANCISCO VA MEDICAL
CENTER
SAN FRANCISCO, CA 94143

FEINSTEIN, MATTHEW JOEL, MD *
ASSISTANT PROFESSOR
DIVISION OF CARDIOLOGY
DEPARTMENT OF MEDICINE
FEINBERG SCHOOL OF MEDICINE
NORTHWESTERN UNIVERSITY
EVANSTON, IL 60208

FORONJY, ROBERT F, MD *
ASSOCIATE PROFESSOR
CHIEF OF PULMONARY AND CRITICAL CARE MEDICINE
DIVISION OF PULMONARY AND CRITICAL CARE MEDICINE
DEPARTMENT OF MEDICINE
SUNY DOWNSTATE MEDICAL CENTER
BROOKLYN, NY 11203

HASTURK, HATICE, PHD, DDS *
ASSOCIATE MEMBER AND DIRECTOR
CENTER FOR CLINICAL AND TRANSLATIONAL RESEARCH
THE FORSYTH INSTITUTE
CAMBRIDGE, MA 02142

HULGAN, TODD M, MD *
ASSOCIATE PROFESSOR
DIVISION OF INFECTIOUS DISEASES
DEPARTMENT OF MEDICINE
VANDERBILT UNIVERSITY MEDICAL CENTER
NASHVILLE, TN 37203

JANKOWSKI, CATHERINE M, PHD *
ASSOCIATE PROFESSOR
DIVISION OF GERIATRIC MEDICINE
COLLEGE OF NURSING AND SCHOOL OF MEDICINE
UNIVERSITY OF COLORADO
AURORA, CO 80045

KANTOR, RAMI, MD
PROFESSOR
DIVISION OF INFECTIOUS DISEASES
DEPARTMENT OF MEDICINE
BROWN UNIVERSITY
PROVIDENCE, RI 02906

KWARA, AWEWURA JACOB, MBBS
ASSOCIATE PROFESSOR
DIVISION OF INFECTIOUS DISEASES & GLOBAL MEDICINE
DEPARTMENT OF MEDICINE
COLLEGE OF MEDICINE
UNIVERSITY OF FLORIDA
GAINESVILLE, FL 32610

LEE, HA YOUN, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR MICROBIOLOGY
AND IMMUNOLOGY
KECK SCHOOL OF MEDICINE
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA 90089

LING, BINHUA, PHD, MD *
ASSOCIATE PROFESSOR
DIVISION OF COMPARATIVE PATHOLOGY
TULANE NATIONAL PRIMATE RESEARCH CENTER
COVINGTON, LA 70433

LONDON, EDYTHE D, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY
AND BIOBEHAVIORAL SCIENCES
SCHOOL OF MEDICINE
UNIVERSITY OF CALIFORNIA, LOS ANGELES
LOS ANGELES, CA 90024

MARRA, CHRISTINA M, MD
PROFESSOR
DEPARTMENT OF NEUROLOGY
HARBORVIEW MEDICAL CENTER
UNIVERSITY OF WASHINGTON
SEATTLE, WA 98104

NAGGIE, SUSANNA, MD
ASSOCIATE PROFESSOR
DIVISION OF INFECTIOUS DISEASES
DEPARTMENT OF MEDICINE
SCHOOL OF MEDICINE
DUKE UNIVERSITY
DURHAM, NC 27705

NDHLOVU, LISHOMWA C, MD, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF TROPICAL MEDICINE, MEDICAL
MICROBIOLOGY, AND PHARMACOLOGY
SCHOOL OF MEDICINE
UNIVERSITY OF HAWAII AT MANOA
HONOLULU, HI 96813

OFOTOKUN, IGHOVWERHA, MD
PROFESSOR
DIVISION OF INFECTIOUS DISEASES
DEPARTMENT OF MEDICINE
EMORY UNIVERSITY
ATLANTA, GA 30303

PAUL, MARY E, MD *
ASSOCIATE PROFESSOR OF PEDIATRICS
DEPARTMENT OF PUBLIC HEALTH SCIENCES
BAYLOR COLLEGE OF MEDICINE
TEXAS CHILDREN'S HOSPITAL
HOUSTON, TX 77030

PECK, ROBERT N, MD *
ASSISTANT PROFESSOR
CENTER FOR GLOBAL HEALTH
JOAN AND SANFORD I. WEILL DEPARTMENT OF MEDICINE
WEILL CORNELL MEDICAL COLLEGE
NEW YORK, NY 10065

RATCLIFFE, SARAH J, PHD
PROFESSOR AND VICE CHAIR FOR RESEARCH
DEPARTMENT OF PUBLIC HEALTH SCIENCES
UNIVERSITY OF VIRGINIA
CHARLOTTESVILLE, VA 22908

SAGAR, MANISH, MD
ASSOCIATE PROFESSOR
DIVISION OF INFECTIOUS DISEASES
SCHOOL OF MEDICINE
BOSTON UNIVERSITY
BOSTON, MA 02118

SARAFIANOS, STEFAN, PHD
PROFESSOR AND ASSOCIATE DIRECTOR
LABORATORY OF BIOMEDICAL PHARMACOLOGY
EMORY UNIVERSITY
ATLANTA, GA 30322

THAMES, APRIL D, PHD *
ASSOCIATE PROFESSOR
CLINICAL NEUROPSYCHOLOGIST
DEPARTMENT OF PSYCHOLOGY
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA 90089

VINCENT, KATHLEEN LISTIAK, MD *
ASSOCIATE PROFESSOR
DEPARTMENT OF OBSTETRICS AND
GYNECOLOGY
UNIVERSITY OF TEXAS MEDICAL BRANCH
GALVESTON, TX 77555-0587

WELSH, DAVID A, MD *
PROFESSOR
DEPARTMENT OF INTERNAL MEDICINE
SCHOOL OF MEDICINE
LOUISIANA STATE UNIVERSITY
NEW ORLEANS, LA 70112

WOOLS-KALOUSTIAN, KARA KAY, MD
PROFESSOR
DIVISION OF INFECTIOUS DISEASES
DEPARTMENT OF MEDICINE
SCHOOL OF MEDICINE
INDIANA UNIVERSITY
INDIANAPOLIS, IN 46202

WU, CHAODONG, PHD, MD *
ASSOCIATE PROFESSOR
DEPARTMENT OF NUTRITION AND FOOD SCIENCE
TEXAS A&M UNIVERSITY
COLLEGE STATION, TX 77843

WYATT, CHRISTINA M, MD *
ASSOCIATE PROFESSOR
DIVISION OF NEPHROLOGY
DUKE CLINICAL RESEARCH INSTITUTE
DUKE UNIVERSITY SCHOOL OF MEDICINE
DURHAM, NC 27705

YOTEBIENG, MARCEL, MD, PHD *
ASSISTANT PROFESSOR
DEPARTMENT OF EPIDEMIOLOGY
COLLEGE OF PUBLIC HEALTH
OHIO STATE UNIVERSITY
COLUMBUS, OH 43210

SCIENTIFIC REVIEW OFFICER

VATAKIS, DIMITRIOS NIKOLAOS, PHD
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

EXTRAMURAL SUPPORT ASSISTANT

IM, CHRISTINE
ADMINISTRATIVE ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.