FDP Cost Reimbursement Subaward

Federal Awarding Agency: National Institutes of Health (NIH)

Pass-Through Entity (PTE):	**Subrecipient:**
The University of Texas Health Science Center at San Antonio	City of Laredo
PTE PI: Gabriel de Erausquin	Sub PI: Richard Chamberlain
PTE Federal Award No: 5 U19 AG076581-02	Subaward No: 176522/176151

Project Title: Interactions of SARS-CoV-2 infection and genetic variation on the risk of cognitive decline and Alzheimer's disease in Ancestral and Admixed Populations

Subaward Budget Period: Start: 08/01/2024 End: 07/31/2025	Amount Funded This Action (USD): $ 224,786.00
Estimated Period of Performance: Start: 08/15/2023 End: 07/31/2028	Incrementally Estimated Total (USD): $

Terms and Conditions

1. PTE hereby awards a cost reimbursable subaward, (as determined by 2 CFR 200.331), to Subrecipient. The Statement of Work and budget for this Subaward are as shown in Attachment 5. In its performance of Subaward work, Subrecipient shall be an independent entity and not an employee or agent of PTE.

2. Subrecipient shall submit invoices not more often than monthly and not less frequently than quarterly for allowable costs incurred. Upon the receipt of proper invoices, the PTE agrees to process payments in accordance with this Subaward and 2 CFR 200.305. All invoices shall be submitted using Subrecipient's standard invoice, but at a minimum shall include current and cumulative costs (including cost sharing), breakdown by major cost category, Subaward number, and certification, as required in 2 CFR 200.415(a). Invoices that do not reference PTE Subaward number shall be returned to Subrecipient. Invoices and questions concerning invoice receipt or payments shall be directed to the party's Financial Contact, shown in Attachment 3A.

3. A final statement of cumulative costs incurred, including cost sharing, marked "FINAL" must be submitted to PTE's Financial Contact, as shown in Attachment 3A, not later than 60 days after the final Budget Period end date. The final statement of costs shall constitute Subrecipient's final financial report.

4. All payments shall be considered provisional and are subject to adjustment within the total estimated cost in the event such adjustment is necessary as a result of an adverse audit finding against the Subrecipient.

5. Matters concerning the technical performance of this Subaward shall be directed to the appropriate party's Principal Investigator as shown in Attachments 3A and 3B. Technical reports are required as shown in Attachment 4.

6. Matters concerning the request or negotiation of any changes in the terms, conditions, or amounts cited in this Subaward, and any changes requiring prior approval, shall be directed to the PTE's Authorized Official Contact and the Subrecipient's Authorized Official Contact shown in Attachments 3A and 3B. Any such change made to this Subaward requires the written approval of each party's Authorized Official as shown in Attachments 3A and 3B.

7. The PTE may issue non-substantive changes to the Budget Period(s) and Budget Bilate rally. Unilateral modification shall be considered valid 14 days after receipt unless otherwise indicated by Subrecipient when sent to Subrecipient's Authorized Official Contact, as shown in Attachment 3B.

8. Each party shall be responsible for its negligent acts or omissions and the negligent acts or omissions of its employees, officers, or directors, to the extent allowed by law.

9. Either party may terminate this Subaward with 30 days written notice. Notwithstanding, if the Awarding Agency terminates the Federal Award, PTE will terminate in accordance with Awarding Agency requirements. PTE notice shall be directed to the Authorized Official Contact, and Subrecipient notice shall be directed to the Authorized Official Contact as shown in Attachments 3A and 3B. PTE shall pay Subrecipient for termination costs as allowable under Uniform Guidance, 2 CFR 200, or 45 CFR Part 75 Appendix IX, as applicable

10. By signing this Subaward, including the attachments hereto which are hereby incorporated by reference, Subrecipient certifies that it will perform the Statement of Work in accordance with the terms and conditions of this Subaward and the applicable terms of the Federal Award, including the appropriate Research Terms and Conditions ("RTCs") of the Federal Awarding Agency, as referenced in Attachment 2. The parties further agree that they intend this subaward to comply with all applicable laws, regulations, and requirements.

By an Authorized Official of the PTE:	By an Authorized Official of the Subrecipient:
Rachel E. Schofield D583EC780819486	Joseph Neeb
11/5/2024	10/29/24
Name: Rachel E. Schofield Date	Name: Joseph Neeb Date
Title: Manager, Contracts and Agreements	Title: City Manager

Attest Mario I. Maldonado Jr.
City Secretary

Subaward Number:

Attachment 1
Certifications and Assurances

Certification Regarding Lobbying (2 CFR 200.450)
By signing this Subaward, the Subrecipient Authorized Official certifies, to the best of his/her knowledge and belief, that no Federal appropriated funds have been paid or will be paid, by or on behalf of the Subrecipient, to any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with the awarding of any Federal contract, the making of any Federal grant, the making of any Federal loan, the entering into of any cooperative agreement, and the extension, continuation, renewal, amendment, or modification of any Federal contract, grant, loan, or cooperative agreement in accordance with 2 CFR 200.450.

If any funds other than Federal appropriated funds have been paid or will be paid to any person for influencing or intending to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with this Federal contract, grant, loan, or cooperative agreement, the Subrecipient shall complete and submit Standard Form -LLL, "Disclosure Form to Report Lobbying," to the PTE.

This certification is a material representation of fact upon which reliance was placed when this transaction was made or entered into. Submission of this certification is a prerequisite for making or entering into this transaction imposed by 31 U.S.C. 1352. Any person who fails to file the required certification shall be subject to a civil penalty of not less than $10,000 and not more than $100,000 for each such failure.

Debarment, Suspension, and Other Responsibility Matters (2 CFR 200.214 and 2 CFR 180)
By signing this Subaward, the Subrecipient Authorized Official certifies, to the best of his/her knowledge and belief that neither the Subrecipient nor its principals are presently debarred, suspended, proposed for debarment, declared ineligible or voluntarily excluded from participation in this transaction by any federal department or agency, in accordance with 2 CFR 200.214 and 2 CFR 180.

Audit and Access to Records
Subrecipient certifies that it will provide PTE with notice of any adverse findings which impact this Subaward. Subrecipient certifies compliance with applicable provisions of 2 CFR 200.501-200.521. If Subrecipient is not required to have a Single Audit as defined by 200.501, Awarding Agency requirements, or the Single Audit Act, then Subrecipient will provide notice of the completion of any required audits and will provide access to such audits upon request. Subrecipient will provide access to records as required by parts 2 CFR 200.332 (a)(5), 200.337, and 200.338 as applicable.

Program for Enhancement of Contractor Employee Protections (41 U.S.C 4712)
Subrecipient is hereby notified that they are required to: inform their employees working on any federal award that they are subject to the whistleblower rights and remedies of the program; inform their employees in writing of employee whistleblower protections under 41 U.S.C §4712 in the predominant native language of the workforce; and include such requirements in any agreement made with a subcontractor or subgrantee.

The Subrecipient shall require that the language of the certifications above in this Attachment 1 be included in the award documents for all subawards at all tiers (including subcontracts, subgrants, and contracts under grants, loans, and cooperative agreements) and that all subrecipients shall certify and disclose accordingly.

Use of Name
Neither party shall use the other party’s name, trademarks, or other logos in any publicity, advertising, or news release without the prior written approval of an authorized representative of that party. The parties agree that each party may use factual information regarding the existence and purpose of the relationship that is the subject of this Subaward for legitimate business purposes, to satisfy any reporting and funding obligations, or as required by applicable law or regulation without written permission from the other party. In any such statement, the relationship of the parties shall be accurately and appropriately described.

Prohibition on Certain Telecommunication and Video Surveillance Services or Equipment
Pursuant to 2 CFR 200.216, Subrecipient will not obligate or expend funds received under this Subaward to: (1) procure or obtain; (2) extend or renew a contract to procure or obtain; or (3) enter into a contract (or extend or renew a contract) to procure or obtain equipment, services, or systems that uses covered telecommunications equipment or services (as described in Public Law 115-232, section 889) as a substantial or essential component of any system, or as a critical technology as part of any system.

Attachment 2
Federal Award Terms and Conditions

Subaward Number

Required Data Elements

The data elements required by Uniform Guidance are incorporated in the attached Federal Award.

Awarding Agency Institute (If Applicable)

NATIONAL INSTITUTE ON AGING

Federal Award Issue Date	FAIN	Assistance Listing No.
08/30/24	U19AG076581	93.866

Assistance Listing Program Title (ALPT)

Aging Research

Key Personnel Per NOA

This Subaward Is:

■ Research & Development ■ Subject to FFATA

General Terms and Conditions

By signing this Subaward, Subrecipient agrees to the following:

1. To abide by the conditions on activities and restrictions on expenditure of federal funds in appropriations acts that are applicable to this Subaward to the extent those restrictions are pertinent. This includes any recent legislation noted on the Federal Awarding Agency's website:

   https://grants.nih.gov/policy/PolicyNotices.php

2. 2 CFR 200
3. The Federal Awarding Agency's grants policy guidance, including addenda in effect as of the beginning date of the period of performance or as amended found at:

   https://grants.nih.gov/grants/policy/nihgps/nihgps.pd

4. Applicable Research Terms and Conditions, including any Federal Awarding Agency's Specific Requirements found at:

   https://www.nsf.gov/awards/managing/rtc.jsp except for the following :

   a. No-cost extensions require the written approval of the PTE. Any requests for a no-cost extension shall be directed to the Administrative Contact shown in Attachment 3A, not less than 30 days prior to the desired effective date of the requested change.
   b. Any payment mechanisms and financial reporting requirements described in the applicable Federal Awarding Agency Terms and Conditions and Agency-Specific Requirements are replaced with Terms and Conditions (1) through (4) of this Subaward; and
   c. Any prior approvals are to be sought from the PTE and not the Federal Awarding Agency.
   d. Title to equipment as defined in 2 CFR 200.1 that is purchased or fabricated with research funds or Subrecipient cost sharing funds, as direct costs of the project or program, shall vest in the Subrecipient subject to the conditions specified in 2 CFR 200.313.
   e. Prior approval must be sought for a change in Subrecipient PI or change in Key Personnel (defined as listed on the NOA).

5. Treatment of program income: Additive

Special Terms and Conditions:

Data Sharing and Access:
Subrecipient agrees to comply with the Federal Awarding Agency's data sharing and/or access requirements as reflected in the NOA or the Federal Awarding Agency's standard terms and conditions as referenced in General Terms and Conditions 1-4 above.

No additional requirements

Data Rights:
Subrecipient grants to PTE the right to use data created in the performance of this Subaward solely for the purpose of and only to the extent required to meet PTE's obligations to the Federal Government under its PTE Federal Award.

Copyrights:

Subrecipient Grants to PTE an irrevocable, royalty-free, non-transferable, non-exclusive right and license to use, reproduce, make derivative works, display, and perform publicly any copyrights or copyrighted material (including any computer software and its documentation and/or databases) first developed and delivered under this Subaward solely for the purpose of and only to the extent required to meet PTE's obligations to the Federal Government under its PTE Federal Award.

Subrecipient grants to PTE the right to use any written progress reports and deliverables created under this Subaward solely for the purpose of and only to the extent required to meet PTE's obligations to the Federal Government under its Federal Award.

Promoting Objectivity in Research (COI):
Subrecipient must designate herein which entity's Financial Conflicts of Interest policy (COI) will apply: Subrecipient

If applying its own COI policy, by execution of this Subaward, Subrecipient certifies that its policy complies with the requirements of the relevant Federal Awarding Agency as identified herein: NIH - 42 CFR Part 50 Subpart F

Subrecipient shall report any financial conflict of interest to PTE's Administrative Representative or COI contact, as designated on Attachment 3A. Any financial conflicts of interest identified shall, when applicable, subsequently be reported to Federal Awarding Agency. Such report shall be made before expenditure of funds authorized in this Subaward and within 45 days of any subsequently identified COI.

Work Involving Human or Vertebrate Animals (Select Applicable Options)

☐ No Human or Vertebrate Animals

☒ Human Subjects

IRB Prior to execution of this agreement and annually thereafter

☐ Vertebrate Animals

The PTE requires verification of IRB and/or IACUC approval be sent to the *Administrative Contact* *as required above:*

Subrecipient agrees that any non-exempt human and/or vertebrate animal research protocol conducted under this Subaward shall be reviewed and approved by the appropriate Institutional Review Board (IRB) and/or its Institutional Animal Care and Use Committee (IACUC), as applicable and that it will maintain current and duly approved research protocols for all periods of the Subaward involving human and/or vertebrate animal research. Subrecipient certifies that the appropriate IRB and/or IACUC are in full compliance with applicable state and federal laws and regulations. The Subrecipient certifies that any submitted IRB / IACUC approval represents a valid, approved protocol that is entirely consistent with the Project associated with this Subaward. In no event shall Subrecipient invoice or be reimbursed for any human or vertebrate animals related expenses incurred in a period where any applicable IRB / IACUC approval is not properly in place.

Human Subjects Data (Select One) Applicable

Human Subjects Data will be exchanged under this Subaward (check all that apply):

☒ From Subrecipient to PTE

☒ From PTE to Subrecipient

The PTE will set forth the terms of the exchange of Human Subjects Data (Select One):

In Attachment 7.

This section left intentionally blank

Additional Terms

Only if authorized by NIH, carryforward from Year 1 to Year 2 will be added, and an amendment issued for those additional funds.

Subaward Number:

Attachment 3A

Pass-Through Entity (PTE) Contacts

PTE Information

Entity Name:

Legal Address: 7703 Floyd Curl Drive
MC 7828, San Antonio, TX 78229-3901

Website: http://research.uthscsa.edu/osp/

PTE Contacts

Central Email: grants@uthscsa.edu

Principal Investigator Name:

Email: deerausquing@uthscsa.edu Telephone Number: 210-450-8694

Administrative Contact Name: Post Award Specialist

Email: grants@uthscsa.edu Telephone Number: 210-567-2340

COI Contact email (if different to above): coi@uthscsa.edu

Financial Contact Name: Post Award Specialist

Email: grants@uthscsa.edu Telephone Number: 210-567-2340

Email invoices? Yes No Invoice email (if different): subaward-invoices@uthscsa.edu

Authorized Official Name: Chris G. Green, CPA

Email: grants@uthscsa.edu Telephone Number: 210-567-2340

PI Address:

7703 Floyd Curl Drive
MC 7828, San Antonio, TX 78229-3901

Administrative Address:

Office of Sponsored Programs
7703 Floyd Curl Drive
MC 7828, San Antonio, TX 78229-3901

Invoice Address:

subaward-invoices@uthscsa.edu

Attachment 3B

Subrecipient Contacts

Subaward Number:

Subrecipient Information for FFATA reporting

Entity's UEI Name: City of Laredo

EIN No.: 74-6001573

Institution Type: Non-Domestic (non-US) Entity

UEI: HWX7C56NNUV1

Currently registered in SAM.gov: Yes No

Exempt from reporting executive compensation: Yes No *(if no, complete 3Bpg2)*

Parent UEI:

This section for U.S. Entities:

Congressional District: 028

Zip Code Look-up

Zip Code+4: 78040-4040

Place of Performance Address

2600 Cedar Ave.
Laredo, TX 78040

Subrecipient Contacts

Central Email:

Website: https://www.cityoflaredo.com/

Principal Investigator Name:

Email: rchamberla@ci.laredo.tx.us

Telephone Number: 956-795-4918

Administrative Contact Name: Erika Martinez

Email: emartinez8@ci.laredo.tx.us

Telephone Number: 956-795-4922

Financial Contact Name: Jose Magana

Email: jmagana@ci.laredo.tx.us

Telephone Number: 956-791-7433

Invoice Email: jmagana@ci.laredo.tx.us

Authorized Official Name: Joseph Neeb

Email: jneeb@ci.laredo.tx.us

Telephone Number: 956-791-7302

Legal Address:

1110 Houston St.
Laredo, TX 78040

Administrative Address:

2600 Cedar Ave.
Laredo, TX 78040

Payment Address:

P.O. Box 579
Laredo, TX 78040

Attachment 3B-2

Highest Compensated Officers

Subaward Number:

Subrecipient:

Institution Name:

PI Name:

Highest Compensated Officers

The names and total compensation of the five most highly compensated officers of the entity(ies) must be listed if the entity in the preceding fiscal year received 80 percent or more of its annual gross revenues in Federal awards; and $25,000,000 or more in annual gross revenues from Federal awards; and the public does not have access to this information about the compensation of the senior executives of the entity through periodic reports filed under section 13(a) or 15(d) of the Securities Exchange Act of 1934 (15 U.S.C. §§ 78m(a), 78o(d)) or section 6104 of the Internal Revenue Code of 1986. See FFATA § 2(b)(1) Internal Revenue Code of 1986.

Officer 1 Name:

Officer 1 Compensation:

Officer 2 Name:

Officer 2 Compensation:

Officer 3 Name:

Officer 3 Compensation:

Officer 4 Name:

Officer 4 Compensation:

Officer 5 Name:

Officer 5 Compensation:

Subaward Number:

Attachment 4
Reporting and Prior Approval Terms

Subrecipient agrees to submit the following reports (PTE contacts are identified in Attachment 3A):

Technical Reports:

☐ Monthly technical/progress reports will be submitted to the PTE's Administrative Contact within 15 days of of the end of the month.

☐ Quarterly technical/progress reports will be submitted within 30 days after the end of each project quarter to the PTE's Administrative Contact.

☒ Annual technical / progress reports will be submitted within 60 days prior to the end of each budget period to the PTE's Administrative Contact. Such report shall also include a detailed budget for the next Budget Period, updated other support for key personnel, certification of appropriate education in the conduct of human subject research of any new key personnel, and annual IRB or IACUC approval, if applicable.

☒ A Final technical/progress report will be submitted to the PTE's Administrative Contact within 60 days of the end of the Project Period or after termination of this award, whichever comes first.

☒ Technical/progress reports on the project as may be required by PTE's Administrative Contact in order for the PTE to satisfy its reporting obligations to the Federal Awarding Agency.

Prior Approvals:

Carryover:

Carryover is restricted for this subaward by the: Federal Awarding Agency

Carryover instructions and requirements are as stated by the Federal Awarding Agency guidance or as shown below.

Submit carryover requests to the Administrative Contact.

Other Reports:

☒ In accordance with 37 CFR 401.14, Subrecipient agrees to notify both the Federal Awarding Agency via iEdison and PTE's Administrative Contact within 60 days after Subrecipient's inventor discloses invention(s) in writing to Subrecipient's personnel responsible for patent matters. The Subrecipient will submit a final invention report using Federal Awarding Agency specific forms to the PTE's Administrative Contact within 60 days of the end of the Project Period to be included as part of the PTE's final invention report to the Federal Awarding Agency.

A negative report is required: Upon Request

☐ Property Inventory Report (only when required by Federal Awarding Agency), specific requirements below.

Additional Technical and Reporting Requirements:

Subaward Number:

Attachment 5
Statement of Work, Cost Sharing, Indirects & Budget

Statement of Work

Below Attached, 1 pages

If award is FFATA eligible and SOW exceeds 4000 characters, include a *Subrecipient Federal Award Project Description*

Budget Information

Indirect Information	Indirect Cost Rate (IDC) Applied	10 %	**Cost Sharing**	No
Rate Type:	Modified Total Direct Costs		If Yes, include Amount: $	

Budget Details

Below Attached, 5 pages

Budget Totals

Direct Costs	$	204,351.00
Indirect Costs	$	20,435.00
Total Costs	$	224,786.00

All amounts are in United States Dollars

SOW

Dr. Chamberlin will be responsible for supervising the clinical coordinators. Clinical Coordinators will be responsible for scheduling all subjects and coordinating timely data collection from our clinicians

OMB Number: 4040-0010
Expiration Date: 12/31/2022

FINAL

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

UEI*: HWX7C56NNUV1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: City of Laredo

Start Date*: 08-01-2024 **End Date*:** 07-31-2025 **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.	Dr	Richard		Chamberlain		Sub Award PD/ PI	0.00	0.01					0.00

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

Additional Senior Key Persons: File Name: **Total Senior/Key Person** **0.00**

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						
2	Research Assistants	24.0	0.0	0.0	119,567.00	59,784.00	179,351.00
2	**Total Number Other Personnel**					**Total Other Personnel**	**179,351.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**179,351.00**

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

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

UEI*: HWX7C56NNUV1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: City of Laredo

Start Date*: 08-01-2024 **End Date*:** 07-31-2025 **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)	0.00
2. Foreign Travel Costs	0.00
Total Travel Cost	**0.00**

E. Participant/Trainee Support Costs		**Funds Requested ($)***
1. Tuition/Fees/Health Insurance		0.00
2. Stipends		0.00
3. Travel		0.00
4. Subsistence		0.00
5. Other:		
0 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

UEI*: HWX7C56NNUV1

Budget Type*: ❍ Project ● Subaward/Consortium

Enter name of Organization: City of Laredo

Start Date*: 08-01-2024 **End Date*:** 07-31-2025 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
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. Participant Support	25,000.00
9.	0.00
10.	0.00
11.	0.00
12.	0.00
13.	0.00
14.	0.00
15.	0.00
16.	0.00
17.	0.00
Total Other Direct Costs	**25,000.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**204,351.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1. MTDC	10.0	204,351.00	20,435.00
		Total Indirect Costs	**20,435.00**

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) Joseph Neeb, jneeb@ci.laredo.tx.us, 1110 Houston 78040.

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**224,786.00**

J. Fee	Funds Requested ($)*
	0.00

K. Total Costs and Fee	Funds Requested ($)*
	224,786.00

L. Budget Justification* File Name: LHD Budget Justification.pdf

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

Budget Justification

Dr. Richard Chamberlain (.01CM) is the Director of the City of Laredo Public Health Department and an Adjunct Professor of Public Health at Texas A&M International University. Dr. Chamberlain will serve as the overall supervisor of this project and monitor the progress of enrollment in the City of Laredo. No salary requested.

TBD Research Assistants (both at 12 CM, 100% FTE) will be responsible for identifying and enrolling eligible participants in the study.

Patient support costs ($25,000) are requested to reimburse participants for travel to the LHD for study related procedures.

Attachment 6

Notice of Award (NOA) and any additional documents

The following pages include the NOA and if applicable any additional documentation referenced throughout this Subaward.

Not incorporating the NOA or any additional documentation to this Subaward.

National Institutes of Health
NATIONAL INSTITUTE ON AGING

Notice of Award
FAIN# U19AG076581
Federal Award Date
08/30/2024

Recipient Information

1. Recipient Name
THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO
7703 FLOYD CURL DR
SAN ANTONIO, TX 78229

2. Congressional District of Recipient
20

3. Payment System Identifier (ID)
1741586031A3

4. Employer Identification Number (EIN)
741586031

5. Data Universal Numbering System (DUNS)
800772162

6. Recipient's Unique Entity Identifier
C3KXNLTAAY98

7. Project Director or Principal Investigator
GABRIEL Alejandro DE ERAUSQUIN, MD (Contact)
Professor Of Neurology And Distinguished University Chair For Research In Alzheimer's And Neurogenerative Diseases
deerausquing@uthscsa.edu
214-450-8694

8. Authorized Official
Chris G. Green CPA

Federal Agency Information

9. Awarding Agency Contact Information
JEFFREY BALL

NATIONAL INSTITUTE ON AGING
ballj@nia.nih.gov
301-496-1472

10. Program Official Contact Information
Marilyn Miller
Health Scientist Administrator
NATIONAL INSTITUTE ON AGING
millerm@nia.nih.gov
(301)496-9350

Federal Award Information

11. Award Number
5U19AG076581-02

12. Unique Federal Award Identification Number (FAIN)
U19AG076581

13. Statutory Authority
42 USC 241 31 USC 6305 42 CFR 52

14. Federal Award Project Title
Interactions of SARS-CoV-2 infection and genetic variation on the risk of cognitive decline and Alzheimer's disease in Ancestral and Admixed Populations

15. Assistance Listing Number
93.866

16. Assistance Listing Program Title
Aging Research

17. Award Action Type
Non-Competing Continuation

18. Is the Award R&D?
Yes

Summary Federal Award Financial Information	
19. Budget Period Start Date 08/01/2024 **– End Date** 07/31/2025	
20. Total Amount of Federal Funds Obligated by this Action	$8,610,822
20 a. Direct Cost Amount	$7,563,907
20 b. Indirect Cost Amount	$1,046,915
21. Authorized Carryover	
22. Offset	
23. Total Amount of Federal Funds Obligated this budget period	$8,610,822
24. Total Approved Cost Sharing or Matching, where applicable	$0
25. Total Federal and Non-Federal Approved this Budget Period	$8,610,822
26. Project Period Start Date 08/15/2023 **– End Date** 07/31/2028	
27. Total Amount of the Federal Award including Approved Cost Sharing or Matching this Project Period	$17,335,980

28. Authorized Treatment of Program Income
Additional Costs

29. Grants Management Officer - Signature
Jeni Smits

30. Remarks

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

SECTION I – AWARD DATA – 5U19AG076581-02

Principal Investigator(s):
GABRIEL Alejandro DE ERAUSQUIN (contact), MD
Gabriela Gonzalez Aleman
THOMAS F. PATTERSON, MD
Sudha Seshadri, MD
Mindy Katz, MPH

Award e-mailed to: nihgrants@uthscsa.edu

Dear Authorized Official:

The National Institutes of Health hereby awards a grant in the amount of $8,610,822 (see "Award Calculation" in Section I and "Terms and Conditions" in Section III) to UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 42 CFR 52 and is subject to the requirements of this statute and regulation and of other referenced, incorporated or attached terms and conditions.

Acceptance of this award, including the "Terms and Conditions," is acknowledged by the recipient when funds are drawn down or otherwise requested from the grant payment system.

Each publication, press release, or other document about research supported by an NIH award must include an acknowledgment of NIH award support and a disclaimer such as "Research reported in this publication was supported by the National Institute On Aging of the National Institutes of Health under Award Number U19AG076581. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health." Prior to issuing a press release concerning the outcome of this research, please notify the NIH awarding IC in advance to allow for coordination.

Award recipients must promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct and reporting of research funded under NIH awards will be free from bias resulting from an Investigator's Financial Conflict of Interest (FCOI), in accordance with the 2011 revised regulation at 42 CFR Part 50 Subpart F. The Institution shall submit all FCOI reports to the NIH through the eRA Commons FCOI Module. The regulation does not apply to Phase I Small Business Innovative Research (SBIR) and Small Business Technology Transfer (STTR) awards. Consult the NIH website http://grants.nih.gov/grants/policy/coi/ for a link to the regulation and additional important information.

If you have any questions about this award, please direct questions to the Federal Agency contacts.

Sincerely yours,

Jeni Smits
Grants Management Officer
NATIONAL INSTITUTE ON AGING

Additional information follows

Cumulative Award Calculations for this Budget Period (U.S. Dollars)

Salaries and Wages	$1,175,747
Fringe Benefits	$353,470
Personnel Costs (Subtotal)	$1,529,217
Consultant Services	$4,000
Materials & Supplies	$20,000
Travel	$42,000
Other	$305,280
Subawards/Consortium/Contractual Costs	$5,645,292
Publication Costs	$11,000
ADP/Computer Services	$7,118
Federal Direct Costs	$7,563,907
Federal F&A Costs	$1,046,915
Approved Budget	$8,610,822
Total Amount of Federal Funds Authorized (Federal Share)	$8,610,822
TOTAL FEDERAL AWARD AMOUNT	$8,610,822
AMOUNT OF THIS ACTION (FEDERAL SHARE)	$8,610,822

SUMMARY TOTALS FOR ALL YEARS (for this Document Number)		
YR	**THIS AWARD**	**CUMULATIVE TOTALS**
2	$8,610,822	$8,610,822
3	$5,888,441	$5,888,441
4	$5,797,392	$5,797,392
5	$4,801,440	$4,801,440

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

Fiscal Information:

Payment System Identifier:	1741586031A3
Document Number:	UAG076581A
PMS Account Type:	P (Subaccount)
Fiscal Year:	2024

IC	CAN	2024	2025	2026	2027
AG	8034655	$8,610,822	$5,888,441	$5,797,392	$4,801,440

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project

NIH Administrative Data:
PCC: 3EGEGMM / **OC**: 41029 / **Released**: 08/29/2024
Award Processed: 08/30/2024 12:17:55 AM

SECTION II – PAYMENT/HOTLINE INFORMATION – 5U19AG076581-02

For payment and HHS Office of Inspector General Hotline information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III – STANDARD TERMS AND CONDITIONS – 5U19AG076581-02

This award is based on the application submitted to, and as approved by, NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Award.
b. Conditions on activities and expenditure of funds in other statutory requirements, such as those included in appropriations acts.
c. 45 CFR Part 75.
d. National Policy Requirements and all other requirements described in the NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.

e. Federal Award Performance Goals: As required by the periodic report in the RPPR or in the final progress report when applicable.
f. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(See NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Research and Development (R&D): All awards issued by the National Institutes of Health (NIH) meet the definition of "Research and Development" at 45 CFR Part§ 75.2**.** As such, auditees should identify NIH awards as part of the R&D cluster on the Schedule of Expenditures of Federal Awards (SEFA). The auditor should test NIH awards for compliance as instructed in Part V, Clusters of Programs. NIH recognizes that some awards may have another classification for purposes of indirect costs. The auditor is not required to report the disconnect (i.e., the award is classified as R&D for Federal Audit Requirement purposes but non-research for indirect cost rate purposes), unless the auditee is charging indirect costs at a rate other than the rate(s) specified in the award document(s).

This institution is a signatory to the Federal Demonstration Partnership (FDP) Phase VII Agreement which requires active institutional participation in new or ongoing FDP demonstrations and pilots.

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

This grant is excluded from Streamlined Noncompeting Award Procedures (SNAP).

This award is subject to the requirements of 2 CFR Part 25 for institutions to obtain a unique entity identifier (UEI) and maintain an active registration in the System for Award Management (SAM). Should a consortium/subaward be issued under this award, a UEI requirement must be included. See http://grants.nih.gov/grants/policy/awardconditions.htm for the full NIH award term implementing this requirement and other additional information.

This award has been assigned the Federal Award Identification Number (FAIN) U19AG076581. Recipients must document the assigned FAIN on each consortium/subaward issued under this award.

Based on the project period start date of this project, this award is likely subject to the Transparency Act subaward and executive compensation reporting requirement of 2 CFR Part 170. There are conditions that may exclude this award; see http://grants.nih.gov/grants/policy/awardconditions.htm for additional award applicability information.

In accordance with P.L. 110-161, compliance with the NIH Public Access Policy is now mandatory. For more information, see NOT-OD-08-033 and the Public Access website: http://publicaccess.nih.gov/.

Recipients must administer the project in compliance with federal civil rights laws that prohibit discrimination on the basis of race, color, national origin, disability, age, and comply with applicable conscience protections. The recipient will comply with applicable laws that prohibit discrimination on the basis of sex, which includes discrimination on the basis of gender identity, sexual orientation, and pregnancy. Compliance with these laws requires taking reasonable steps to provide meaningful access to persons with limited English proficiency and providing programs that are accessible to and usable by persons with disabilities. The HHS Office for Civil Rights provides guidance on complying with civil rights laws enforced by HHS. See https://www.hhs.gov/civil-rights/for-providers/provider-obligations/index.html and https://www.hhs.gov/.

- Recipients of FFA must ensure that their programs are accessible to persons with limited English proficiency. For guidance on meeting the legal obligation to take reasonable steps to ensure meaningful access to programs or activities by limited English proficient individuals, see https://www.hhs.gov/civil-rights/for-individuals/special-topics/limited-english-proficiency/fact-sheet-guidance/index.html and https://www.lep.gov.
- For information on an institution's specific legal obligations for serving qualified individuals with disabilities, including providing program access, reasonable modifications, and to provide effective communication, see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html.
- HHS funded health and education programs must be administered in an environment free of sexual harassment; see https://www.hhs.gov/civil-rights/for-individuals/sex-discrimination/index.html.

For information about NIH's commitment to supporting a safe and respectful work environment, who to contact with questions or concerns, and what NIH's expectations are for institutions and the individuals supported on NIH-funded awards, please see https://grants.nih.gov/grants/policy/harassment.htm.

- For guidance on administering programs in compliance with applicable federal religious nondiscrimination laws and applicable federal conscience protection and associated anti-discrimination laws, see https://www.hhs.gov/conscience/conscience-protections/index.html and https://www.hhs.gov/conscience/religious-freedom/index.html.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts with cumulative total value greater than $10,000,000 must report and maintain information in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently the Federal Awardee Performance and Integrity Information System (FAPIIS)). Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75. This term does not apply to NIH fellowships.

Treatment of Program Income:
Additional Costs

SECTION IV – AG SPECIFIC AWARD CONDITIONS – 5U19AG076581-02

Clinical Trial Indicator: No
This award does not support any NIH-defined Clinical Trials. See the NIH Grants Policy Statement Section 1.2 for NIH definition of Clinical Trial.

RESTRICTION: Funds are restricted pending the National Institute on Aging's receipt and acceptance of the completed Section G.10. c and spend down plan as requested August 23, 2024.

Funding for this award has been provided by Alzheimer's Disease Initiative funds.

The requested budget was considered and determined not to represent significant re-budgeting. Therefore, categorical amounts reflect the direct and facilities and administrative cost (F&A) levels previously recommended for the current year. Funds may be re-budgeted between direct costs and F&A costs, consistent with applicable cost principles and institutional and policy requirements for prior approval.

As appropriate, the awardee is required to follow the sharing plan(s) for unique research resources (i.e. Data, Model Organism, Genomic Data, or other) associated with this project and may not implement any changes to the plan(s) without the written prior approval of the National Institute of Aging (NIA).

In accordance with the Notice: NOT-OD-02-017 entitled, "GRADUATE STUDENT COMPENSATION" published on December 10, 2001, in the NIH Guide for Grants and Contracts, total direct costs (salary, fringe benefits and tuition remission) for graduate students are provided at a level not to exceed the NIH maximum allowable amount (zero level of the Ruth L. Kirschstein National Research Service Award stipend in effect at the time of the competing award). Support recommended for future years has been adjusted accordingly, if applicable. The full guide Notice describing the level of compensation allowed for a graduate student can be found at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-017.html

Dissemination of study data will be in accordance with the Recipient's accepted genomic data sharing plan as stated in the application received 5/25/2022. Failure to adhere to the sharing plan as mutually agreed upon by the Recipient and the NIH/NIA may result in Enforcement Actions as described in the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps/index.htm.

Additional information regarding NIH's Genomic Data Sharing Policy can be found at: https://gds.nih.gov.

In keeping with NOT-OD-06-054 (**http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-054.html**), as this grant has multiple Principal Investigators (PIs), although the signatures of the PIs are not required on prior approval requests submitted to the agency, the grantee institution must secure and retain the signatures of all of the PIs within their own internal processes.

This award reflects the acceptance of the single Institutional Review Board (sIRB) plan submitted with the application dated 5/25/2022. Any changes to this plan require the written prior approval of the National Institute on Aging.

This award includes funds awarded for consortium activity with Indiana University (Admin. Core Sub 1).

This award includes funds awarded for consortium activity with University of Miami (Admin. Core Sub 2).

This award includes funds awarded for consortium activity with University of Pennsylvania (Admin. Core Sub 3).

This award includes funds awarded for consortium activity with University of Pennsylvania (Admin. Core Sub 4).

This award includes funds awarded for consortium activity with Albert Einstein College of Medicine (Admin. Core Sub 5).

This award includes funds awarded for consortium activity with Alzheimer's Disease and Related Disorder Association, Inc. (Admin. Core Sub 6).

This award includes funds awarded for consortium activity with Albert Einstein College of Medicine (Core 3 Sub 1).

This award includes funds awarded for consortium activity with University of Washington (Core 3 Sub 2).

This award includes funds awarded for consortium activity with University of Ibadan (Core 3 Sub 3).

This award includes funds awarded for consortium activity with Foundation for the Fight against Neurological and Psychiatric Disorders in Minorities.

This award includes funds awarded for consortium activity with Washington University (Project 1 Sub 1).

This award includes funds awarded for consortium activity with University of Texas Rio Grande Valley (Con Project 1).

Consortiums are to be established and administered as described in the NIH Grants Policy Statement (NIH GPS). The referenced section of the NIH Grants Policy Statement, 2017 is available at: http://grants.nih.gov/grants/policy/nihgps/HTML5/section_15/15_consortium_agreements.htm

This award is issued as a Cooperative Agreement, a financial assistance mechanism in which substantial NIH scientific and/or programmatic involvement is anticipated in the performance of the activity. This award is subject to the Terms and Conditions of Award as set forth in the SPECIAL REQUIREMENTS section of PAR-19-374: Complex Integrated Multi-Component Projects in Aging Research (U19 Clinical Trial Optional) (nih.gov) which are hereby incorporated by reference as special terms and conditions of this award.

This RFA may be accessed at: PAR-19-374: Complex Integrated Multi-Component Projects in Aging Research (U19 Clinical Trial Optional) (nih.gov)

Cooperative Agreement Terms and Conditions of Award
The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (DHHS) grant administration regulations at 45 CFR Part 75, and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities.
Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.
The PD(s)/PI(s) will have the primary responsibility for:

- coordinating the Research Project;

- retaining primary responsibility for the planning, directing, and executing the proposed scientific activities;
- ensuring that all projects involving human or animal subjects have the appropriate clearances (e.g., IRB, FWA, IACUC, human subject's research training, and other required documentation) prior to implementation;
- submitting yearly progress reports for the Project; and
- keeping the NIA Program Official and NIA Project Scientist apprised of any potential impediments to execution of the goals of the Project; and
- Awardees will retain custody of and have primary rights to the data and software developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies.

NIH staff have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below:

- The role of the NIA/NIH Project Scientist in the cooperative agreement is to support and encourage the recipient's activities by substantial involvement as partners and facilitators in the process without assuming responsibilities that remain with the PD(s)/PI(s).
- The NIA Project Scientist will monitor the progress of the Research Project, help coordinate research approaches, and contribute to the shaping of research projects or approaches as warranted. The NIA Project Scientist will support and facilitate this process but will not direct it.
- The NIA Project Scientist will retain the option to recommend the withholding or reduction of support from any cooperative agreement that substantially fails to achieve its goals according to the milestones agreed to at the time of the award or fails to comply with the Terms and Conditions of the award.

Additionally, an agency program official or IC program director will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice.
Areas of Joint Responsibility include:

- The NIA Project Scientist will coordinate with the PD(s)/PI(s) to facilitate the achievement of program goals.

Dr. Jonathan King, NIA Health Scientist Administrator will be the NIA Project Scientist for this award and will be responsible for scientific involvement during conduct of this activity, through technical assistance, advice and coordination, assisting in those aspects of the award as described below. The NIA Project Scientist will monitor the deposition of samples into NCRAD to ensure that NIA-funded investigators have appropriately deposited data and have properly acknowledged the use of the ADSP data in the publication of their work. The NIA Project Scientist will ensure that quality-control-checked, harmonized data are released in a timely fashion through NIAGADS or other NIA-approved data sharing sites. The NIA Project Scientist will review protocols for workflow and data sharing before they can be implemented. The NIA Project Scientist will be a non-voting "ex officio" member of the Executive Committee and all key subcommittees.
Additionally, the NIA Program Director, **Dr. Marilyn Miller,** will be responsible for the normal scientific and programmatic stewardship of the award.

Dispute Resolution:
Any disagreements that may arise in scientific or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the Steering Committee chosen without NIH staff voting, one NIH designee, and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and DHHS regulation 45 CFR Part 16.

The milestones negotiated with the NIA for the -01 Notice of Award remain unchanged.

Title: Interactions of SARS-CoV-2 infection and genetic variation on the risk of cognitive decline and Alzheimer's disease in Ancestral and Admixed Populations (ISAVRAD)

Principal Investigators: Gabriel A. de Erausquin (Contact), Mindy Katz, Thomas F. Patterson, Sudha Seshadri.

U19 Milestones

Interactions of SARS-CoV-2 infection and genetic variation on the risk of cognitive decline and Alzheimer's disease in Ancestral and Admixed Populations (ISAVRAD)

ISAVRAD is fully integrated with, and complementary to, the Alzheimer's Disease Sequencing Project Follow-Up Study 2.0 (ADSP FUS 2.0). Indeed, ISAVRAD is fully aligned with the goals of ADSP FUS 2.0 because it will conduct research by multidisciplinary teams of investigators to develop leading-edge, *innovative gene x environment approaches* for the analysis of whole genome sequence (WGS) in a *uniquely ethnic/racial diverse longitudinal sample* of cases unrelated to each other with available comparable controls. Genetic and phenotype (including brain imaging and biomarkers) data from ISAVRAD participants *will make full use of the ADSP infrastructure and provide financial support* the National Central Cell Repository for Alzheimer's Disease (NCRAD); the American Genome Center at the Uniformed Services University for the Health Sciences (TAGC/USUHS) and the Center for Genome Technology at the University of Miami Miller School of Medicine (CGT/UMMSM); the Genome Center for Alzheimer's Disease (GCAD); and the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Raw data will be shared using the standard agreement and procedures set up by ADSP as described below. ISAVRAD has the following **overall goals:**

1. *Determine whether cognitive/neuropsychiatric sequelae of SARS-CoV-2 infection place individuals (particularly older adults) at increased risk of Alzheimer's disease or related dementias (ADRD), earlier onset, or a faster course of illness.*
2. *Explore environmental, genetic, clinical and neuroimaging predictors of risk and resilience in order to design secondary prevention and treatment strategies.*
3. *Describe the longitudinal course, epidemiological risk/resiliency factors, and environmental interactions predictive of cognitive decline and progress to cognitive decline or ADRD following SARS-CoV-2 infection in adults over 65 years of age from ancestral and admixed populations.*
4. *Assess gene x environment interactions predictive of risk and resilience to cognitive decline and progression to ADRD in ancestral and admixed populations, using whole genome sequencing from Amerindian, African, and US-based admixed (Hispanic and African American) newly recruited cohorts*
5. *Describe the neural signatures of COVID-19 on neuroimaging networks associated with neurological symptoms (anosmia and cognitive impairment) as predictors of progression to cognitive decline or ADRD in ancestral and admixed populations.*
6. *The ultimate end of ISAVRAD is to deepen the understanding of the pathophysiology of both long-term sequelae of COVID-19 and ADRD and thus lead to novel and successful preventative strategies for both diseases and for syndemic interactions between them.*

.

The ISAVRAD Consortium encompasses five data collection sites each focused on specific under-represented populations:

Site	Location	Population Focus	Institutional Partner
Jujuy	Argentina	Amerindian	Fundacion FULTRA
Ibadan	Nigeria	Yoruba	University of Ibadan
San Antonio/Laredo	Texas	Mexican-American	University of Texas Health San Antonio
Bronx	New York	Hispanic and African American	Einstein School of Medicine
Seattle	Washington	Non-tribal Amerindian	University of Washington

Milestones: Below are the milestones for Cores 1-4 and Projects 1-3. We list the goal and aims of each Core 1nd project followed by a Summary Table of Deliverables over the five (5) years. The detailed five (5) years of milestones of each Core and project follow the Summary Tables of Deliverables.

Core 1 Milestones

MPIs: Gabriel A. de Erausquin, MD, PhD (Contact) Co-I Gabriela Gonzalez Aleman PhD
Sudha Seshadri, MD
Thomas Patterson, MD
Mindy Katz, MSc

SPECIFIC AIMS: CORE 1 (Administrative Core)

The overall goal of **Core 1** is to coordinate and provide the support for all ISAVRAD activities and interactions. ISAVRAD is a multiple PI (MPI) application headed by 4 well established investigators, all with an extensive track record in ancestral populations research, infectious diseases, genetic/genomics and/or AD research. The central goals of **Core 1** are the successful development, implementation and coordination of a multi-site international collaborative effort involving shared operations and ethical standards, harmonized recruitment and assessment methods, and biomaterial acquisition, transfers and banking in a longitudinal diverse cohort of elderly individuals with variable exposure to SARS-CoV-2 infection. **Core 1**, in collaboration with **Core 4**, will manage the transfer of samples from collection sites to the pertinent Cores, manage relationships between the sequencing centers and DNA repositories, oversee compliance and harmonization at international sites, and coordinate the activities of the Cores, including their data/materials exchanges with the scientific Projects. Five established committees will oversee the activities of **Core 1**: Leadership, Long- Term Planning, Scientific Administrative, Fiscal & Management Oversight, and Publications. The AC *will make full use of the ADSP infrastructure and establish subawards, scope of work, data and material transfer agreements and pipelines with* NCRAD, TAGC/USUHS, CGT/UMMSM, and NIAGADS. All harmonized data will be deposited with the Genome Center for Alzheimer's Disease (GCAD). The aims of **Core 1** are four-fold.

AIM 1: Manage the ISAVRAD and its internal relationships with the leaders of the Cores and Projects, including the leaders at the 5 data collection sites. Specifically, the AC will establish and revisit timely program priorities, optimize the sharing of resources among Cores and Projects, review data and specimen management needs, communicate scientific advances, promote scientific relationships and collaborations with other aging programs within the ISAVRAD network, and oversee ethical and legal issues.

AIM 2: Manage ISAVRAD relationships external to ISAVRAD, including communicating with the External Advisory Committee members, communicating, coordinating and collaborating with other aging studies to identify new and emerging areas of scientific inquiry relevant to the goals of ISAVRAD; oversee the preparation of annual progress reports for the National Institute on Aging; oversee the sharing of resources with investigators at outside institutions (e.g., data/material usage agreements); promote outreach to community residents at all recruitment sites to disseminate current topics on health, ADRD, and lifestyles, and disseminate scientific findings to the research community.

Aim 3: Coordinate and work with the Clinical, Neuroimaging, and Data Management and Statistics Cores to ensure harmonization of recruitment, data collection, data storage and management, and data/materials transfers throughout the ISAVRAD consortium.

Aim 4: Oversee faculty development activities at each academic center affiliated with this U-19, including structured in-person mentoring and attendance at meetings/conferences.

CORE 1: ADMINISTRATIVE	Not Started	In Progress	Completed

Year 1 Deliverables			
Completion of NIH Clearance form, DDA, DSP, GDS, MTAs. DUAs and IRBs			
Completion of sub-contracts			
Establishment of all committees membership, schedules and monitoring			
Set up collaboration call schedule and first face-to- face/hybrid meeting of investigators			
Year 2 Deliverables			
Continue financial monitoring of sub-contract			
Assist sites with any IRB issues or updates			
Quality assurance of all committee meetings and ISAVRAD-wide and EAC meetings			
Training of postdoctoral fellows			
Year 3 Deliverables			
Continue financial monitoring of sub-contract			
Assist sites with any IRB issues or updates			
Quality assurance of all committee meetings and ISAVRAD-wide and EAC meetings			
Training of postdoctoral fellows			
Oversee dissemination of Results to Scientific Community			
Year 4 Deliverables			
Continue financial monitoring of sub-contract			
Assist sites with any IRB issues or updates			
Quality assurance of all committee meetings and ISAVRAD-wide and EAC meetings			
Training of postdoctoral fellows			
Oversee dissemination of Results to Scientific Community			
Year 5 Deliverables			
Continue financial monitoring of sub-contract			
Assist sites with any IRB issues or updates			
Quality assurance of all committee meetings and ISAVRAD-wide and EAC meetings			
Training of postdoctoral fellows			

Core 1 Year 1 Milestones

Milestone #1-1 **Aim 1a: Completion of NIH Foreign Clearance forms**
Criteria for Success: Sending completed forms to NIA.
Rationale: These forms must be completed as part of funding.
Progress: *Completed.*

Milestone #1-2 **Aim 1b: Completion of the Data Sharing Plans and Genomic Data Sharing agreements.**
Criteria for Success: All regulatory documents from all sites are signed.
Rationale: Regulatory documents are required to allow for the transfer of samples and data.
Progress: *Left to complete. Several agreements are already in place and ~350 DNA samples have already been transferred from Argentina (FULTRA) to CGT/UMMSM, quality controlled and sequenced. Additional ~500 samples are currently being processed for transferring and processing. Other sites are initiating the process for obtaining signatures. The Nigeria site requires IRB approval.*

Milestone #1-3	**Aim 1c: Completion of Material Transfer Agreements and Data Use Agreements**
Criteria for Success:	All inter-institutional agreements are signed.
Rationale:	Regulatory documents are required to allow for the transfer of samples and data.
Progress:	*Left to complete. Agreement between FULTRA and CGT/UMMSM already in place. Completion of others anticipated within 2 months of release of funds. Some sites won't execute without NOA*

Milestone #1-4	**Aim 1d: Assist sites as they develop their IRB protocols and coordinate with all sites for modifications.**
Criteria for Success:	IRBs protocols are approved.
Rationale:	No research can take place without appropriate IRBs in place.
Progress:	*Left to complete. Most sites have their approval in place. Core 1 is working with Nigeria to establish theirs.*

Milestone #1-5	**Aim 1e**: **Execute sub-contracts.**
Criteria for Success:	All financial agreements are in place.
Rationale:	Financial agreements must be in place so that contracting institutions can be paid.
Progress:	*Left to complete. All sites have been vendorized. Once NOA is issued, agreements will be executed.*

Milestone #1-6	**Aim 1f: Provide ongoing financial oversight**
Criteria for Success:	Spending is monitored, and PIs are kept of apprised of financial situation.
Rationale:	Spending must take place as planned without going over or under allotted amounts.
Progress:	*Left to complete. This will begin once money is transferred and will continue throughout grant award period.*

Milestone #1-7	**Aim 2a: Establish schedule for PI meetings and hold and record such meetings.**
Criteria for Success:	Establishing a time for semi-monthly video meetings of all PIs, holding the meetings, and recording and sharing minutes of meetings with all PIs.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Left to complete. PIs are being queried for meeting times. Anticipate holding first meeting within 1 month of release of funds.*

Milestone #1-8	**Aim 2b: Semi-annual in-person meetings at the AAIC and ADSP conferences with all attending investigators.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project, and in-person meetings allow for more interaction and build upon the relationships established through videoconferencing.
Progress:	*Left to complete. AAIC is being in held in Amsterdam Netherlands, in July. ADSP is typically held in the spring.*

Milestone #1-9	**Aim 2c: Coordinate and oversee training of post-doctoral fellows and junior faculty.**

Criteria for Success:	Post-doctoral fellows are assigned one to each of the 3 Projects and will work directly with PIs on analysis of primary data, elaboration of reports for publication, drafting of manuscripts, presentation of data at scientific meetings and seminars, and collaborative efforts within and outside the ISAVRAD Consortium. Junior faculty have been assigned leadership roles in several internal committees and within each of the 4 Cores; they will work under the mentorship of senior investigators on development of leadership skills, grant and publication writing and establishment of independent research programs.
Rationale:	Having appropriately trained investigators will increase the likelihood of success of this proposal as well as future applications.
Progress:	*Left to complete. A training program is being developed. Post-doctoral fellows will be identified with-in the first several months of grant initiation.*

Milestone #1-10	**Aim 3a: Schedule and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications Committees meetings as scheduled.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and requires global oversight in addition to the more granular oversight focused on specific aspects of the management.
Progress:	*Left to complete. First meetings to be held after initiation of grant.*

Milestone #1-11	**Aim 3b: Establish External Advisory Committee (EAC) and schedule meetings.**
Criteria for Success:	Individuals for the EAC are identified, agree to serve, and first meeting is scheduled.
Rationale:	Non-ISAVRAD investigators provide an impartial evaluation of the work as well as assisting in identifying independent solutions to roadblocks.
Progress:	*Left to complete. As soon as NOA is released, potential members will be invited to serve. The first meeting will be held within the first 2 months of the funding period.*

Milestone #1-12	**Aim 3c: Schedule an annual in-person meeting of EAC, MPIs and relevant staff as well as to three annual video conferences.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Left to complete. EAC will be established as soon as NOA is received and EAC and MPIs will then be polled for potential dates.*

Milestone #1-13	**Aim 3d: Schedule an annual annual program review at an agreed upon time with NIA, and quarterly meetings with NIA program staff to update progress.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent oversight and monitoring by NIA is instrumental for its success and to overcome hurdles.
Progress:	*Left to complete. Dates will be established as soon as NOA is*

received and NIA and MPIs will then be polled for potential dates.

Milestone #1-14 **Aim 4a: ensure the dissemination of research and track publications and presentations at scientific meetings.**
Criteria for Success: Data is shared to required sites and publications and presentations at scientific meetings when appropriate.
Rationale: Dissemination of research is critical for the field to advance.
Progress: *Left to complete. Dissemination will occur when results are available.*

Year 1 Deliverables:

- **Completion of NIH Clearance form, DSP, GDS, MTAs. DUAs and IRBs**
- **Completion of sub-contracts**
- **Establish the EAC committees**
- **Set up collaboration call schedule and first face-to-face/hybrid meeting of investigators.**

Core 1 Year 2 Milestones

Milestone #2-1 **Aim 1a: Completion of NIH Foreign Clearance forms**
Criteria for Success: Sending completed forms to NIA.
Rationale: These forms must be completed as part of funding.
Progress: *Completed in year 1.*

Milestone #2-2 **Aim 1b: Completion of the DSP and GDS.**
Criteria for Success: All regulatory documents from all sites are signed.
Rationale: Regulatory documents are required to allow for the transfer of samples and data.
Progress: *Completed in year 1.*

Milestone #2-3 **Aim 1c: Completion of MTAs and DUAs**
Criteria for Success: All inter-institutional agreements are signed.
Rationale: Regulatory documents are required to allow for the transfer of samples and data.
Progress: *Completed in year 1.*

Milestone #2-4 **Aim 1d: Assist sites as they develop their IRB protocols and coordinate with all sites for modifications.**
Criteria for Success: Assist sites with modifications.
Rationale: No research can take place without appropriate IRBs in place.
Progress: *This will take place throughout years 2-5.*

Milestone #2-5 **Aim 1e**: **Execute sub-contracts.**
Criteria for Success: All financial agreements are in place.
Rationale: Financial agreements must be in place so that contracting institutions can be paid.
Progress: *Completed in year 1*

Milestone #2-6 **Aim 1f: Provide ongoing financial oversight**
Criteria for Success: Spending is monitored, and PIs are kept of apprised of financial situation.
Rationale: Spending must take place as planned without going over or under allotted amounts.

Progress:	*Left to complete. Oversight will continue throughout years 2-5.*
Milestone #2-7	**Aim 2a: Establish schedule for PI meetings and hold and record such meetings.**
Criteria for Success:	Holding the meetings and recording and sharing minutes of meetings with all PIs.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*
Milestone #2-8	**Aim 2b: Semi-annual in-person meetings at the AAIC and ADSP conferences with all attending investigators.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project, and in-person meetings allow for more interaction and build upon the relationships established through videoconferencing.
Progress:	*Meetings will be held during years 2-5.*
Milestone #2-9	**Aim 2c: Coordinate and oversee training of post-doctoral fellows and junior faculty.**
Criteria for Success:	Post-doctoral fellows are assigned one to each of the 3 Projects and will work directly with PIs on analysis of primary data, elaboration of reports for publication, drafting of manuscripts, presentation of data at scientific meetings and seminars, and collaborative efforts within and outside the ISAVRAD Consortium. Junior faculty have been assigned leadership roles in several internal committees and within each of the 4 Cores; they will work under the mentorship of senior investigators on development of leadership skills, grant and publication writing and establishment of independent research programs..
Rationale:	Having appropriately trained investigators will increase the likelihood of success of this proposal as well as future applications.
Progress:	*Training will occur during years 2-5.*
Milestone #2-10	**Aim 3a: Schedule and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications Committees meetings.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and requires global oversight in addition to the more granular oversight of the bi-monthly meetings.
Progress:	*Meetings will be held during years 2-5.*
Milestone #2-11	**Aim 3b: Establish EAC and schedule meetings.**
Criteria for Success:	Individuals for the EAC identified were identified in year 1; meetings are scheduled and held.
Rationale:	Non-ISAVRAD investigators provide an impartial evaluation of the work as well as assisting in identifying independent solutions to roadblocks.
Progress:	*Meetings will be held during years 2-5.*
Milestone #2-12	**Aim 3c: Schedule an annual in-person meeting of EAC, MPIs and relevant staff as well as to three annual video conferences.**

Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*

Milestone #2-13	**Aim 3d: Schedule an annual annual program review at an agreed upon time with NIA, and quarterly meetings with NIA program staff to update progress.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent oversight and monitoring by NIA is instrumental for its success and to overcome hurdles.
Progress:	*Left to complete. Dates will be established as soon as NOA is received and NIA and MPIs will then be polled for potential dates.*

Milestone #2-14	**Aim 4a: Ensure the dissemination of research and track publications and presentations at scientific meetings.**
Criteria for Success:	Data is shared to required sites and publications and presentations at scientific meetings when appropriate.
Rationale:	Dissemination of research is critical for the field to advance.
Progress:	*Dissemination will occur throughout years 2-5.*

Year 2 deliverables:

- **Continue financial monitoring of sub-contract**
- **Assist sites with any IRB issues or updates**
- **Establish Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications Committees Meetings and annual EAC meetings and tri-annual EAC video conference**
- **Training of postdoctoral fellows and junior faculty**

Core 1 Year 3 Milestones

Milestone #3-1	**Aim 1d: Assist sites as they develop their IRB protocols and coordinate with all sites for modifications.**
Criteria for Success:	Assist sites with modifications.
Rationale:	No research can take place without appropriate IRBs in place.
Progress:	*This will take place throughout years 2-5.*

Milestone #3-2	**Aim 1f: Provide ongoing financial oversight**
Criteria for Success:	Spending is monitored, and PIs are kept of apprised of financial situation.
Rationale:	Spending must take place as planned without going over or under allotted amounts.
Progress:	*Left to complete. Oversight will continue throughout years 2-5.*

Milestone #3-3	**Aim 2a: Establish schedule for PI meetings and hold and record such meetings.**
Criteria for Success:	Holding the meetings and recording and sharing minutes of meetings with all PIs.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*

Milestone #3-4	**Aim 2b: Semi-annual in-person meetings at the AAIC and**

	ADSP conferences with all attending investigators.
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project, and in-person meetings allow for more interaction and build upon the relationships established through videoconferencing.
Progress:	*Meetings will be held during years 2-5.*
Milestone #3-5	**Aim 2c: Coordinate and oversee training of post-doctoral fellows and junior faculty.**
Criteria for Success:	Post-doctoral fellows are assigned one to each of the 3 Projects and will work directly with PIs on analysis of primary data, elaboration of reports for publication, drafting of manuscripts, presentation of data at scientific meetings and seminars, and collaborative efforts within and outside the ISAVRAD Consortium. Junior faculty have been assigned leadership roles in several internal committees and within each of the 4 Cores; they will work under the mentorship of senior investigators on development of leadership skills, grant and publication writing and establishment of independent research programs..
Rationale:	Having appropriately trained investigators will increase the likelihood of success of this proposal as well as future applications.
Progress:	*Training will occur during years 2-5.*
Milestone #3-6	**Aim 3a: Schedule and hold Schedule and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications Committee meetings.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and requires global oversight in addition to the more granular oversight of the bi-monthly meetings.
Progress:	*Meetings will be held during years 2-5.*
Milestone #3-7	**Aim 3b: Schedule and hold EAC live and video meetings.**
Criteria for Success:	Individuals for the EAC identified were identified in year 1; meetings are scheduled and held.
Rationale:	Non-ISAVRAD investigators provide an impartial evaluation of the work as well as assisting in identifying independent solutions to roadblocks.
Progress:	*Meetings will be held during years 2-5.*
Milestone #3-8	**Aim 3c: Schedule an annual in-person meeting of EAC, MPIs and relevant staff as well as to three annual video conferences.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*
Milestone #3-9	**Aim 3d: Schedule an annual annual program review at an agreed upon time with NIA, and quarterly meetings with NIA program staff to update progress.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent oversight and monitoring by NIA is instrumental for its success and to overcome hurdles.

Progress:	*Left to complete. Dates will be established as soon as NOA is received and NIA and MPIs will then be polled for potential dates.*
Milestone #3-10	**Aim 4a: Ensure the dissemination of research and track publications and presentations at scientific meetings.**
Criteria for Success:	Data is shared to required sites and publications and presentations at scientific meetings when appropriate.
Rationale:	Dissemination of research is critical for the field to advance.
Progress:	*Dissemination will occur throughout years 2-5.*

Year 3 deliverables:

- **Continue financial monitoring of sub-contract**
- **Assist sites with any IRB issues or updates**
- **Establish and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications meetings and EAC meeting and (3) video conferences**
- **Training of postdoctoral fellows and junior faculty**
- **Oversee dissemination of Results to Scientific Community.**

Core 1 Year 4 Milestones

Milestone #4-1	**Aim 1d: Assist sites as they develop their IRB protocols and coordinate with all sites for modifications.**
Criteria for Success:	Assist sites with modifications.
Rationale:	No research can take place without appropriate IRBs in place.
Progress:	*This will take place throughout years 2-5.*
Milestone #4-2	**Aim 1f: Provide ongoing financial oversight**
Criteria for Success:	Spending is monitored, and PIs are kept of apprised of financial situation.
Rationale:	Spending must take place as planned without going over or under allotted amounts.
Progress:	*Left to complete. Oversight will continue throughout years 2-5.*
Milestone #4-3	**Aim 2a: Establish schedule for PI meetings and hold and record such meetings.**
Criteria for Success:	Holding the meetings and recording and sharing minutes of meetings with all PIs.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*
Milestone #4-4	**Aim 2b: Semi-annual in-person meetings at the AAIC and ADSP conferences with all attending investigators.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project, and in-person meetings allow for more interaction and build upon the relationships established through videoconferencing.
Progress:	*Meetings will be held during years 2-5.*
Milestone #4-5	**Aim 2c: Coordinate and oversee training of post-doctoral fellows and junior faculty.**
Criteria for Success:	Post-doctoral fellows are assigned one to each of the 3 Projects and will work directly with PIs on analysis of primary data,

elaboration of reports for publication, drafting of manuscripts, presentation of data at scientific meetings and seminars, and collaborative efforts within and outside the ISAVRAD Consortium. Junior faculty have been assigned leadership roles in several internal committees and within each of the 4 Cores; they will work under the mentorship of senior investigators on development of leadership skills, grant and publication writing and establishment of independent research programs..

Rationale: Having appropriately trained investigators will increase the likelihood of success of this proposal as well as future applications.

Progress: *Training will occur during years 2-5.*

Milestone #4-6 **Aim 3a: Schedule and hold bi-monthly Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications committee meetings.**

Criteria for Success: Meetings are scheduled and held.

Rationale: This is a complex project and requires global oversight in addition to the more granular oversight of the bi-monthly meetings.

Progress: *Meetings will be held during years 2-5.*

Milestone #4-7 **Aim 3b: Establish EAC and schedule meetings.**

Criteria for Success: Individuals for the EAC identified were identified in year 1; meetings are scheduled and held.

Rationale: Non-ISAVRAD investigators provide an impartial evaluation of the work as well as assisting in identifying independent solutions to roadblocks.

Progress: *Meetings will be held during years 2-5.*

Milestone #4-8 **Aim 3c: Schedule an annual in-person meeting of EAC, MPIs and relevant staff as well as to three annual video conferences.**

Criteria for Success: Meetings are scheduled and held.

Rationale: This is a complex project and frequent communication if paramount to its success.

Progress: *Meetings will be held during years 2-5.*

Milestone #4-9 **Aim 3d: Schedule an annual annual program review at an agreed upon time with NIA, and quarterly meetings with NIA program staff to update progress.**

Criteria for Success: Meetings are scheduled and held.

Rationale: This is a complex project and frequent oversight and monitoring by NIA is instrumental for its success and to overcome hurdles.

Progress: *Left to complete. Dates will be established as soon as NOA is received and NIA and MPIs will then be polled for potential dates.*

Milestone #4-10 **Aim 4a: Ensure the dissemination of research and track publications and presentations at scientific meetings.**

Criteria for Success: Data is shared to required sites and publications and presentations at scientific meetings when appropriate.

Rationale: Dissemination of research is critical for the field to advance.

Progress: *Dissemination will occur throughout years 2-5.*

Year 4 deliverables:

- **Continue financial monitoring of sub-contract**
- **Assist sites with any IRB issues or updates**
- **Establish and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications committees meetings and annual EAC meetings and (3) video conferences**
- **Training of postdoctoral fellows and junior faculty**
- **Oversee dissemination of results to the Scientific Community**

Core 1 Year 5 Milestones	
Milestone #5-1	**Aim 1d: Assist sites as they develop their IRB protocols and coordinate with all sites for modifications.**
Criteria for Success:	Assist sites with modifications.
Rationale:	No research can take place without appropriate IRBs in place.
Progress:	*This will take place throughout years 2-5.*
Milestone #5-2	**Aim 1f: Provide ongoing financial oversight**
Criteria for Success:	Spending is monitored, and PIs are kept of apprised of financial situation.
Rationale:	Spending must take place as planned without going over or under allotted amounts.
Progress:	*Left to complete. Oversight will continue throughout years 2-5.*
Milestone #5-3	**Aim 2a: Establish schedule for PI meetings and hold and record such meetings.**
Criteria for Success:	Holding the meetings and recording and sharing minutes of meetings with all PIs.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*
Milestone #5-4	**Aim 2b: Semi-annual in-person meetings at the AAIC and ADSP conferences with all attending investigators.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project, and in-person meetings allow for more interaction and build upon the relationships established through videoconferencing.
Progress:	*Meetings will be held during years 2-5.*
Milestone #5-5	**Aim 2c: Coordinate and oversee training of post-doctoral fellows.**
Criteria for Success:	Post-doctoral fellows are assigned one to each of the 3 Projects and will work directly with PIs on analysis of primary data, elaboration of reports for publication, drafting of manuscripts, presentation of data at scientific meetings and seminars, and collaborative efforts within and outside the ISAVRAD Consortium. Junior faculty have been assigned leadership roles in several internal committees and within each of the 4 Cores; they will work under the mentorship of senior investigators on development of leadership skills, grant and publication writing and establishment of independent research programs..
Rationale:	Having appropriately trained investigators will increase the likelihood of success of this proposal as well as future

	applications.
Progress:	*Training will occur during years 2-5.*
Milestone #5-6	**Aim 3a: Schedule and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications meetings.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and requires global oversight in addition to the more granular oversight of the bi-monthly meetings.
Progress:	*Meetings will be held during years 2-5.*
Milestone #5-7	**Aim 3b: Establish EAC and schedule meetings.**
Criteria for Success:	Individuals for the EAC identified were identified in year 1; meetings are scheduled and held.
Rationale:	Non-ISAVRAD investigators provide an impartial evaluation of the work as well as assisting in identifying independent solutions to roadblocks.
Progress:	*Meetings will be held during years 2-5.*
Milestone #5-8	**Aim 3c: Schedule an annual in-person meeting of EAC, MPIs and relevant staff as well as to three annual video conferences.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent communication if paramount to its success.
Progress:	*Meetings will be held during years 2-5.*
Milestone #5-9	**Aim 3d: Schedule an annual annual program review at an agreed upon time with NIA, and quarterly meetings with NIA program staff to update progress.**
Criteria for Success:	Meetings are scheduled and held.
Rationale:	This is a complex project and frequent oversight and monitoring by NIA is instrumental for its success and to overcome hurdles.
Progress:	*Left to complete. Dates will be established as soon as NOA is received and NIA and MPIs will then be polled for potential dates.*
Milestone #5-10	**Aim 4a: Ensure the dissemination of research and track publications and presentations at scientific meetings.**
Criteria for Success:	Data is shared to required sites and publications and presentations at scientific meetings when appropriate.
Rationale:	Dissemination of research is critical for the field to advance.
Progress:	*Dissemination will occur throughout years 2-5.*

Year 5 deliverables:

- **Continue financial monitoring of sub-contract**
- **Assist sites with any IRB issues or updates**
- **Establish and hold Leadership, Long-term Planning, Fiscal & Management Oversight, and Publications committees meetings and annual EAC meetings and (3) video conferences**
- **Training of postdoctoral fellows and junior faculty**
- **Oversee dissemination of Results to Scientific Community.**

Core 2 Neuroimaging Milestones

MPIs: Peter T. Fox MD

Co-I

J

inqi Li
Mohamad Habes PhD

P

avel Rodriguez
Geoffrey D. Clarke PhD
Sidath Kumarapperuma PhD

SPECIFIC AIMS: Core 2 (Neuroimaging Core)

Core 2 will manage neuroimaging acquisition, quality control, harmonization, data archiving, and data sharing at all five study sites. Image acquisition, quality control and harmonization strategies will emulate those of ADNI3 and Mark VCID supplemented by team expertise. Minimal data preprocessing will use pipelined approaches, both volumetric and surface-based. Surface-based analyses will emulate Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) protocols, with the expectation that other large studies of the post-acute sequelae of COVID-19 (PASC) will emerge and that ENIGMA community will embrace the challenge of ongoing data exploration, both meta-analytic and mega-analytic.

Aim 1: Image Acquisition, Harmonization and Quality Control. Structural MRI and functional MRI images will be acquired at all five study sites. Structural MRI acquisitions will emulate those of ADNI3, UKBioBank, HCP Lifespan, MarkVCID and GOBS. Functional MRI acquisitions will emulate the latest GOBS. The NIC will coordinate acquisition across sites, including harmonization and quality control.

Aim 2: Image Preprocessing and Pipeline Analytics. NIC will perform post-acquisition quality control, image preprocessing (artifact removal, motion correction, etc.), and run widely used volumetric and surface-based pipeline analyses.

Aim 3: Image Archiving, Access Control, and Sharing. Anonymized volumetric and surfaced-based images (raw and processed), image-derived data (region of interest [ROI] values), and visual-inspection scores will be archived in the XNAT system for sharing. Spreadsheet-compatible data will be provided to the Data Management and Statistics Core (DMSC).

CORE 2 Neuroimaging Core	Not Started	In Progress	Complet
Year 1 Deliverables			
Establish acquisition session harmonization following ADNI procedures, anonymization, data transfer, and MRI Pulse-Sequence Harmonization following ADNI 3 and MarkVCID protocols at 5 sites			
Complete MRI Hardware Harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by imagng of 5 healthy controls applying the post-acquisition QC procedures			
Establish MRI Post-acquisition Harmonization procedures using ComBat.			
Establish acquisition protocols for 18FDG PET according to ADNI3 protocol			
Establish SOPs for Visual Quality Inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross			

structural lesions or volume alterations (MTA, Koedam and Fazekas scores)			
Establish volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); White matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols			
Surface-based pipeline using ENIGMA and Quality control (QC) procedures also following ENIGMA protocols			
Establish fMRI BOLD volumetric and surface-based pipelinefor voxel-based physiological image computation			
Establish Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI Skeletonization pipeline and TRACULA.			
Establish ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures			
Establish image Archiving, Access Control, and Sharing.Anonymized raw and processed volumetric, surface-basedimages,image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data will be provided to the Core 3 (D&S).			
Year 2 Deliverables			
Repeat (ongoing) MRI Hardware Harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures			
Continue MRI Post-acquisition Harmonization procedures using ComBat.			
Initiate Visual Quality Inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores) in Visit 1 and Visit 2 MRI data			
Initiate volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); White matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols in visit 1 and visit 2 MRI data			
Initiate urface-based pipeline using ENIGMA and Quality control (QC) procedures also following ENIGMA protocols in visit 1 and visit 2 MRI data			
Initiate fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in visit 1 and visit 2 MRI data			
Initiate Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI Skeletonization pipeline and TRACULA in visit 1 and visit 2 MRI data			
Initiate ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in visit 1 and visit 2 fMRI and PET data			
Image Archiving, Access Control, and Sharing.Anonymized raw and processed volumetric, surface-basedimages,image-derived data (ROI values) and visual-inspection scores archiving in XNAT for MRI and PET visit 1 and visit 2 MRI data. Spreadsheet-compatible data provided to the Core 3 (D&S).			
Year 3 Deliverables			
Repeat (ongoing) MRI Hardware Harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures			
Continue MRI Post-acquisition Harmonization procedures using ComBat.			
Initiate Visual Quality Inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores) in Visit 2 MRI data			

Initiate volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); White matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols in visit 2 MRI data			
Initiate urface-based pipeline using ENIGMA and Quality control (QC) procedures also following ENIGMA protocols in visit 2 MRI data			
Initiate fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in visit 2 MRI data			
Initiate Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI Skeletonization pipeline and TRACULA in visit 2 MRI data			
Initiate ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in visit 2 fMRI and PET data			
Image Archiving, Access Control, and Sharing.Anonymized raw and processed volumetric, surface-basedimages,image-derived data (ROI values) and visual-inspection scores archiving in XNAT of visit 2 MRI and PET data. Spreadsheet-compatible data provided to the Core 3 (D&S).			
Year 4 Deliverables			
Continue MRI Hardware Harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures			
Continue MRI Post-acquisition Harmonization procedures using ComBat.			
Continue Visual Quality Inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores) in MRI visit 2 data			
Continue volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); White matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols in MRI visit 2 data			
Continue surface-based pipeline using ENIGMA and Quality control (QC) procedures also following ENIGMA protocols in MRI visit 2 data			
Continue fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in MRI visit 2 data			
Continue Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI Skeletonization pipeline and TRACULA in MRI visit 2 data			
Continue ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in fMRI and PET visit 2 data			
Image Archiving, Access Control, and Sharing.Anonymized raw and processed volumetric, surface-basedimages,image-derived data (ROI values) and visual-inspection scores archiving in XNAT of visit 2 MRI and PET data. Spreadsheet-compatible data will be provided to the Core 3 (D&S).			
Year 5 Deliverables			
Establish acquisition session harmonization following ADNI procedures, anonymization, data transfer, and MRI Pulse-Sequence Harmonization following ADNI 3 and MarkVCID protocols at 5 sites			
Continue MRI Post-acquisition Harmonization procedures using ComBat.			
Complete volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); White matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols for visit 2 MRI data			

Complete surface-based pipeline using ENIGMA and Quality control (QC) procedures also following ENIGMA protocols for visit 2 MRI data			
Complete fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in MRI visit 2 data			
Complete Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI Skeletonization pipeline and TRACULA in MRI visit 2 data.			
Complete ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in fMRI and PET visit 2 data			
Complete image Archiving, Access Control, and Sharing.Anonymized raw and processed volumetric, surface-basedimages,image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data will be provided to the Core 3 (D&S).			

Core 2 Year 1 Milestones

Milestone #1-1 **Aim 1 Establish acquisition session harmonization following ADNI procedures, anonymization, data transfer, and MRI Pulse-Sequence harmonization following ADNI 3 and MarkVCID protocols at 5 sites**

Criteria for Success: Completed harmonization and SOPs.

Rationale: High quality comparable imaging data are required for any cohort-wide studies or future comparisons inside or outside of the ISAVRAD consortium.

Progress: *In progress.*

Milestone #1-2 **Aim 1 Complete MRI hardware harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by imagng of 5 healthy controls applying the post-acquisition QC procedures**

Criteria for Success: High reproducibility measured by intraclass correlation (ICC) and Coefficient of Variation (SD/mean*100%). Comparable consistency between sites/vendors examined using the Bland-Altman method (repeatability= 2*1.96*SD) and Pearson correlation.

Rationale: The five sites will employ MRI scanners from 4 vendors and two field strengths,necessitating rigorous harmonization.

Progress: *In progress.*

Milestone #1-3 **Aim 1 Establish MRI post-acquisition harmonization procedures using ComBat.**

Criteria for Success: ComBat harmonization pipelines for ROI-wise harmonization implemented and output provided quarterly to the Core 3 (DM&S) for distribution

Rationale: Heterogeneity across vendors, sequences, imaging sites, and time require further statistical harmonization

Progress: *To be completed.*

Milestone #1-4 **Aim 1 Establish acquisition protocols for ^{18}FDG PET according to ADNI 3 protocol**

Criteria for Success: Completed high quality acquisition ADNI 3 protocols.

Rationale: ADNI 3 provides an accepted standard to allow future

comparisons within and outside of the ISAVRAD consortium.
Progress: *In progress.*

Milestone #1-5 **Aim 2 Establish SOPs for visual quality inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores)**
Criteria for Success: Completed SOPs and personnel training to ensure similar quality and visual interpretation at all sites.
Rationale: Visual inspection by trained technologists and neuroradiologists is standard and required for quality assurance and participant protections.
Progress: *To be completed.*

Milestone #1-6 **Aim 2 Establish volumetric segmentation pipeline; advanced normalization tools; (ANTs); tissue segmentation (FSL); white matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols**
Criteria for Success: Automated pipelines for high quality pre processing established.
Rationale: Basic preprocessing is necessary to minimize artifacts, provide normalized images, and obtain initial segmentation of normal and pathological tissue.
Progress: *To be completed.*

Milestone #1-7 **Aim 2 Surface-based pipeline using ENIGMA and quality control (QC) procedures also following ENIGMA protocols.**
Criteria for Success: Images with adequate quality control and tesselation of white-gray borders, topology correction, surface deformation and parcellation of cerebral cortex**.**
Rationale: Voxel-based analyses require high quality parcellations.
Progress: *To be completed.*

Milestone #1-8 **Aim 2 Establish fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation.**
Criteria for Success: Registered images corrected for head motion, slice timing, susceptibility distortion, confounds and denoising.
Rationale: High quality registered fMRI images are required for voxel-based physiological image computations.
Progress: *To be completed.*

Milestone #1-9 **Aim 2 Establish diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI skeletonization pipeline and TRACULA.**
Criteria for Success: Preprocessed whole-brain average and regional measurements from DTI images including FA, Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD) images.
Rationale: Minimal preprocessing of DTI images is required for anatomical connectivity analysis and comparison with Human Connectome and similar datasets.
Progress: *To be completed.*

Milestone #1-10 **Aim 2 Establish ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures, ^{18}FDG PET volumetric and surface-based measures**

Criteria for Success:	Preprocessed surface maps, regional measures, standardizes mages and statistical maps.
Rationale:	Standardized images will be used as a reference image for PET scans for individual subjects and normalized relative FDG statistical maps calculated according the ADNI 3 protocol.
Progress:	*To be completed.*

Milestone #1-11	**Aim 3 Establish image archiving, access control, and sharing.**
Criteria for Success:	Anonymized raw and processed volumetric, surface-based images, image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data provided to Core 3 (DM&S) for distribution.
Rationale:	To ensure privacy protections while maintaining data integrity and allowing safe and compliant data sharing.
Progress:	*To be completed.*

Year 1 Deliverables:

- **Comprehensive harmonization, image acquisition, quality control, transmission and archiving workflows and pipelines**
- **Comprehensive preprocessing and postprocessing pipelines for MRI and PET data**
- **Initial transfer of MRI and PET data on ~ 2,000 individuals**
- **Archiving of data and distribution of images and metadata to Core 3 (DM&S) and Projects 1-3.**

Core 2 Year 2 Milestones

Milestone #2-1	**Aim 1 Repeat (ongoing) MRI hardware harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures**
Criteria for Success:	High reproducibility measured by intraclass correlation (ICC) and Coefficient of Variation (SD/mean*100%). Comparable consistency between sites/vendors examined using the Bland-Altman method (repeatability= 2*1.96*SD) and Pearson correlation.
Rationale:	The five sites will employ MRI scanners from 4 vendors and two field strengths,necessitating rigorous harmonization..
Progress:	*To be completed.*

Milestone #2-2	**Aim 1 Continue MRI post-acquisition harmonization procedures using ComBat**
Criteria for Success:	ComBat harmonization pipelines for ROI-wise harmonization implemented and output provided quarterly to the Core 3 (DM&S) for distribution
Rationale:	Heterogeneity across vendors, sequences, imaging sites, and time require further statistical harmonization
Progress:	*To be completed.*

Milestone #2-3	**Aim 2 Initiate visual quality inspection for raw image quality, protocolv compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores) in Visit 1 and Visit 2 MRI data**
Criteria for Success:	Completed high quality acquisition ADNI 3 protocols.

Rationale:	ADNI 3 provides an accepted standard to allow future comparisons within and outside of the ISAVRAD consortium.
Progress:	*To be completed.*
Milestone #2-4	**Aim 2 Initiate volumetric segmentation pipeline; advanced normalization tools (ANTs); tissue segmentation (FSL); White matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols in visit 1 and visit 2 MRI data**
Criteria for Success:	Automated pipelines for high quality pre processing established.
Rationale:	Basic preprocessing is necessary to minimize artifacts, provide normalized images, and obtain initial segmentation of normal and pathological tissue.
Progress:	*To be completed.*
Milestone #2-5	**Aim 2 Initiate urface-based pipeline using ENIGMA and quality control (QC) procedures also following ENIGMA protocols in visit 1 and visit 2 MRI data**
Criteria for Success:	Images with adequate quality control and tesselation of white-gray borders, topology correction, surface deformation and parcellation of cerebral cortex**.**
Rationale:	Voxel-based analyses require high quality parcellations.
Progress:	*To be completed.*
Milestone #2-6	**Aim 2 Initiate fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in visit 1 and visit 2 MRI data**
Criteria for Success:	Registered images corrected for head motion, slice timing, susceptibility distortion, confounds and denoising.
Rationale:	High quality registered fMRI images are required for voxel-based physiological image computations.
Progress:	*To be completed.*
Milestone #2-7	**Aim 2 Initiate Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI skeletonization pipeline and TRACULA in visit 1 and visit 2 MRI data**
Criteria for Success:	Preprocessed whole-brain average and regional measurements from DTI images including FA, Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD) images.
Rationale:	Minimal preprocessing of DTI images is required for anatomical connectivity analysis and comparison with Human Connectome and similar datasets.
Progress:	*To be completed.*
Milestone #2-8	**Aim 2 Initiate ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures, 18 FDG PET volumetric and surface-based measures in visit 1 and visit 2 fMRI and PET data**
Criteria for Success:	Preprocessed surface maps, regional measures, standardizes mages and statistical maps.
Rationale:	Standardized images will be used as a reference image for PET scans for individual subjects and normalized relative FDG statistical maps calculated according the ADNI 3 protocol.
Progress:	*To be completed.*

Milestone #2-8	**Image Archiving, Access Control, and Sharing.**
Criteria for Success:	Anonymized raw and processed volumetric, surface-based images, image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data provided to Core 3 (DM&S) for distribution.
Rationale:	To ensure privacy protections while maintaining data integrity and allowing safe and compliant data sharing.
Progress:	*To be completed.*

Year 2 Deliverables

- **Ongoing hardware harmonization, image quality control and oversight of transmission and archiving workflows and pipelines**
- **Ongoing preprocessing and postprocessing pipelines for MRI and PET data**
- **Ongoing transfer of MRI and PET data on ~ 4,300 individuals (visit 1) and ~500 visit 2**
- **Archiving of data and distribution of images and metadata to Core 3 (DM&S) and Projects 1-3.**

Core 2 Year 3 Milestones

Milestone #3-1	**Aim 1 Repeat (ongoing) MRI hardware harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures**
Criteria for Success:	High reproducibility measured by intraclass correlation (ICC) and Coefficient of Variation (SD/mean*100%). Comparable consistency between sites/vendors examined using the Bland-Altman method (repeatability= 2*1.96*SD) and Pearson correlation.
Rationale:	The five sites will employ MRI scanners from 4 vendors and two field strengths,necessitating rigorous harmonization.
Progress:	*To be completed.*
Milestone #3-2	**Aim 1 Continue MRI post-acquisition harmonization procedures using ComBat**
Criteria for Success:	ComBat harmonization pipelines for ROI-wise harmonization implemented and output provided quarterly to the Core 3 (DM&S) for distribution
Rationale:	Heterogeneity across vendors, sequences, imaging sites, and time require further statistical harmonization
Progress:	*To be completed.*
Milestone #3-3	**Aim 2 Initiate visual quality inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores) in Visit 2 MRI data**
Criteria for Success:	Completed high quality acquisition ADNI 3 protocols.
Rationale:	ADNI 3 provides an accepted standard to allow future comparisons within and outside of the ISAVRAD consortium.
Progress:	*To be completed.*
Milestone #3-4	**Aim 2 Initiate volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL);**

	white matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols in visit 2 MRI data
Criteria for Success:	Automated pipelines for high quality pre processing established.
Rationale:	Basic preprocessing is necessary to minimize artifacts, provide normalized images, and obtain initial segmentation of normal and pathological tissue.
Progress:	*To be completed.*
Milestone #3-5	**Aim 2 Initiate urface-based pipeline using ENIGMA and quality control (QC) procedures also following ENIGMA protocols in visit 2 MRI data**
Criteria for Success:	Images with adequate quality control and tesselation of white-gray borders, topology correction, surface deformation and parcellation of cerebral cortex**.**
Rationale:	Voxel-based analyses require high quality parcellations.
Progress:	*To be completed.*
Milestone #3-6	**Aim 2 Initiate fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in visit 2 MRI data**
Criteria for Success:	Registered images corrected for head motion, slice timing, susceptibility distortion, confounds and denoising.
Rationale:	High quality registered fMRI images are required for voxel-based physiological image computations.
Progress:	*To be completed.*
Milestone #3-7	**Aim 2 Initiate diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI skeletonization pipeline and TRACULA in visit 2 MRI data**
Criteria for Success:	Preprocessed whole-brain average and regional measurements from DTI images including FA, Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD) images.
Rationale:	Minimal preprocessing of DTI images is required for anatomical connectivity analysis and comparison with Human Connectome and similar datasets.
Progress:	*To be completed.*
Milestone #3-8	**Aim 2 Initiate ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in visit 2 fMRI and PET data**
Criteria for Success:	Preprocessed surface maps, regional measures, standardizes mages and statistical maps.
Rationale:	Standardized images will be used as a reference image for PET scans for individual subjects and normalized relative FDG statistical maps calculated according the ADNI 3 protocol.
Progress:	*To be completed.*
Milestone #3-9	**Aim 3 Image Archiving, Access Control, and Sharing.**
Criteria for Success:	Anonymized raw and processed volumetric, surface-based images, image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data provided to Core 3 (DM&S) for distribution.
Rationale:	To ensure privacy protections while maintaining data integrity

and allowing safe and compliant data sharing.

Progress: *To be completed.*

Year 3 Deliverables

- **Ongoing hardware harmonization, image quality control and oversight of transmission and archiving workflows and pipelines**
- **Ongoing preprocessing and postprocessing pipelines for MRI and PET data**
- **Ongoing transfer of MRI and PET data on ~ 4,300 individuals (visit 1) and ~2,500 (visit 2) individuals**
- **Archiving of data and distribution of images and metadata to Core 3 (DM&S) and Projects 1-3.**

Core 2 Year 4 Milestones

Milestone #4-1	**Aim 1 Continue MRI hardware harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures**
Criteria for Success:	High reproducibility measured by intraclass correlation (ICC) and Coefficient of Variation (SD/mean*100%). Comparable consistency between sites/vendors examined using the Bland-Altman method (repeatability= 2*1.96*SD) and Pearson correlation.
Rationale:	The five sites will employ MRI scanners from 4 vendors and two field strengths,necessitating rigorous harmonization.
Progress:	*To be completed.*
Milestone #4-2	**Aim 2 Continue MRI hardware harmonization across 5 sites using ADNI phantom images assessed for: signal-to-noise, contrast-to-noise, intensity non-uniformity, and geometric distortion; followed by post-acquisition QC procedures**
Criteria for Success:	ComBat harmonization pipelines for ROI-wise harmonization implemented and output provided quarterly to the Core 3 (DM&S) for distribution
Rationale:	Heterogeneity across vendors, sequences, imaging sites, and time require further statistical harmonization
Progress:	*To be completed.*
Milestone #4-3	**Aim 2 Continue visual quality inspection for raw image quality, protocol compliance, subject position, and acquisition artifacts; visual radiographic reading to identify gross structural lesions or volume alterations (MTA, Koedam and Fazekas scores) in MRI visit 2 data**
Criteria for Success:	Completed high quality acquisition ADNI 3 protocols.
Rationale:	ADNI 3 provides an accepted standard to allow future comparisons within and outside of the ISAVRAD consortium.
Progress:	*To be completed.*
Milestone #4-4	**Aim 2 Continue volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); white matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols in MRI visit 2 data**
Criteria for Success:	Automated pipelines for high quality pre processing established.
Rationale:	Basic preprocessing is necessary to minimize artifacts, provide normalized images, and obtain initial segmentation of normal

and pathological tissue.
Progress: *To be completed.*

Milestone #4-5 **Aim 2 Continue surface-based pipeline using ENIGMA and quality control (QC) procedures also following ENIGMA protocols in MRI visit 2 data**
Criteria for Success: Images with adequate quality control and tesselation of white-gray borders, topology correction, surface deformation and parcellation of cerebral cortex**.**
Rationale: Voxel-based analyses require high quality parcellations.
Progress: *To be completed.*

Milestone #4-6 **Aim 2 Continue fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in MRI visit 2 data**
Criteria for Success: Registered images corrected for head motion, slice timing, susceptibility distortion, confounds and denoising.
Rationale: High quality registered fMRI images are required for voxel-based physiological image computations.
Progress: *To be completed.*

Milestone #4-7 **Aim 2 Continue Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI skeletonization pipeline and TRACULA in MRI visit 2 data**
Criteria for Success: Preprocessed whole-brain average and regional measurements from DTI images including FA, Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD) images.
Rationale: Minimal preprocessing of DTI images is required for anatomical connectivity analysis and comparison with Human Connectome and similar datasets.
Progress: *To be completed.*

Milestone #4-8 **Aim 2 Continue ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in fMRI and PET visit 2 data**
Criteria for Success: Preprocessed surface maps, regional measures, standardizes mages and statistical maps.
Rationale: Standardized images will be used as a reference image for PET scans for individual subjects and normalized relative FDG statistical maps calculated according the ADNI 3 protocol.
Progress: *To be completed.*

Milestone #4-9 **Aim 3 Image Archiving, Access Control, and Sharing.**
Criteria for Success: Anonymized raw and processed volumetric, surface-based images, image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data provided to Core 3 (DM&S) for distribution.
Rationale: To ensure privacy protections while maintaining data integrity and allowing safe and compliant data sharing.
Progress: *To be completed.*

Year 4 Deliverables

- **Ongoing hardware harmonization, image quality control and oversight of**

transmission and archiving workflows and pipelines

- **Ongoing preprocessing and postprocessing pipelines for MRI and PET data**
- **Ongoing transfer of MRI and PET data on ~ 4,300 individuals (visit 1) and ~4,300 (visit 2) individuals**
- **Archiving of data and distribution of images and metadata to Core 3 (DM&S) and Projects 1-3.**

Core 2 Year 5 Milestones	
Milestone #5-1	**Aim 1 Establish acquisition session harmonization following ADNI procedures, anonymization, data transfer, and MRI pulse-sequence harmonization following ADNI 3 and MarkVCID protocols at 5 sites**
Criteria for Success:	High reproducibility measured by intraclass correlation (ICC) and Coefficient of Variation (SD/mean*100%). Comparable consistency between sites/vendors examined using the Bland-Altman method (repeatability= 2*1.96*SD) and Pearson correlation.
Rationale:	The five sites will employ MRI scanners from 4 vendors and two field strengths,necessitating rigorous harmonization.
Progress:	*To be completed.*
Milestone #5.2	**Aim 1 Continue MRI post-acquisition harmonization procedures using ComBat**
Criteria for Success:	ComBat harmonization pipelines for ROI-wise harmonization implemented and output provided quarterly to the Core 3 (DM&S) for distribution
Rationale:	Heterogeneity across vendors, sequences, imaging sites, and time require further statistical harmonization
Progress:	*To be completed.*
Milestone #5.3	**Aim 2 Complete volumetric segmentation pipeline ; advanced normalization tools; (ANTs); tissue segmentation (FSL); white matter hyperintensity (WMH) volumes using MarkVCID-UCD protocols for visit 2 MRI data**
Criteria for Success:	Automated pipelines for high quality pre processing established.
Rationale:	Basic preprocessing is necessary to minimize artifacts, provide normalized images, and obtain initial segmentation of normal and pathological tissue.
Progress:	*To be completed.*
Milestone #5-4	**Aim 2 Complete surface-based pipeline using ENIGMA and quality control (QC) procedures also following ENIGMA protocols for visit 2 MRI data**
Criteria for Success:	Images with adequate quality control and tesselation of white-gray borders, topology correction, surface deformation and parcellation of cerebral cortex**.**
Rationale:	Voxel-based analyses require high quality parcellations.
Progress:	*To be completed.*
Milestone #5-5	**Aim 2 Complete fMRI BOLD volumetric and surface-based pipeline for voxel-based physiological image computation in MRI visit 2 data**
Criteria for Success:	Registered images corrected for head motion, slice timing, susceptibility distortion, confounds and denoising.

Rationale:	High quality registered fMRI images are required for voxel-based physiological image computations.
Progress:	*To be completed.*

Milestone #5-6	**Aim 2 Complete Diffusion tensor imaging volumetric pipeline using FSL and tract-based spatial statistics using the ENIGMA-DTI Skeletonization pipeline and TRACULA in MRI visit 2 data.**
Criteria for Success:	Preprocessed whole-brain average and regional measurements from DTI images including FA, Axial Diffusivity (AD), Radial Diffusivity (RD), and Mean Diffusivity (MD) images.
Rationale:	Minimal preprocessing of DTI images is required for anatomical connectivity analysis and comparison with Human Connectome and similar datasets.
Progress:	*To be completed.*

Milestone #5-7	**Aim 2 Complete ADNI 3 based pipelines for preprocessing and estimation of CBF surface maps and regional measures,18FDG PET volumetric and surface-based measures in fMRI and PET visit 2 data**
Criteria for Success:	Preprocessed surface maps, regional measures, standardizes mages and statistical maps.
Rationale:	Standardized images will be used as a reference image for PET scans for individual subjects and normalized relative FDG statistical maps calculated according the ADNI 3 protocol.
Progress:	*To be completed.*

Milestone #5-8	**Aim 3 Complete image Archiving, Access Control, and Sharing.**
Criteria for Success:	Anonymized raw and processed volumetric, surface-based images, image-derived data (ROI values) and visual-inspection scores archiving in XNAT. Spreadsheet-compatible data provided to Core 3 (DM&S) for distribution.
Rationale:	To ensure privacy protections while maintaining data integrity and allowing safe and compliant data sharing.
Progress:	*To be completed.*

Year 5 Deliverables

- **Complete preprocessing and postprocessing pipelines for MRI and PET data**
- **Complete transfer of MRI and PET data on ~ 4,300 individuals (visit 1) and ~4,300 (visit 2) individuals**
- **Complete archiving of data and distribution of images and metadata to Core 3 (DM&S) and Projects 1-3.**

Core 3 Milestones

MPIs: Meredith Nahm Zozus PhD PhD
Chen-Pin Wang PhD

Co-Is William James Sanns
Jayandra Himali PhD

The Data Management and Statistics Core (DM&SC) is one of 4 Cores supporting the scientific research activities of the four ISAVRAD Program Projects and is responsible for management, reporting and sharing of raw and meta-data generated by the Clinical and Neuroimaging Cores;

from NIA ADSP components (NCRAD, NIAGADS and GCAD); and from ISAVRAD Projects, to allow completion of the proposed aims and foster collaboration within and outside the ISAVRAD network. *Specifically, the DM&SC will work with the NIA funded Phenotype Harmonization Consortium to define common data elements to share with the NIA funded infrastructure and with investigators outside of ISAVRAD*. Led by the two Informatics and Statistics Core leaders for the South Texas Alzheimer's Center, the DM&SC is equipped with advanced informatics, data management, and statistical infrastructure and expertise to meet these specialized needs. Drs Zozus and Sanns boast decades of experience providing comprehensive coordinating center support for clinical studies and offer extensive practical knowledge of regulatory-grade data handling requirements and methods. Drs. Wang and Himali provide design and analysis expertise. The DM&SC will provide reliable processes for the recording, management, storing and sharing of data and metadata within and outside the ISAVRAD network to support the mission of the other cores and foster the completion of the Projects aims and collaborative efforts, with the goals of aligning ISAVRAD data with appropriate standards to maximize data reuse; providing information systems and expert support for data and sample collection and management; and curating and preparing data for external sharing through national repositories.

1. **Align ISAVRAD data with appropriate standards to maximize data reuse, including the ADCs, UDS, the WHO Clinical Characterization CRF, relevant controlled terminology and other data standards**. Pre-existing conditions, signs and symptoms, new diagnoses and complications will be mapped to the MedDRA controlled terminology. MedDRA, or Medical Dictionary for Regulatory Activities, is a clinically validated international medical terminology dictionary-thesaurus used by regulatory authorities and the biopharmaceutical industry. Medications will be mapped to WHODrug Global, the international reference for conventional medicines and herbal remedies across 150 countries and is maintained by the Uppsala Monitoring Centre. Through the five-level Anatomical Therapeutic Chemical (ATC) classification system, active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Thus, WHODrug enables international; data pooling and analysis at multiple levels of granularity. Lab tests and measured physical quantities will be mapped to Logical Observation Identifiers Names and Codes (LOINC) codes. If the need arises, new codes will be requested through the respective Standards Development Organizations (SDOs). International standards for date and time representation and units of measure will be used. Where not otherwise standardized, the Clinical Data Interchange Standards Consortium (CDISC) Clinical Data Acquisition Standards Harmonization (CDASH) and Submission Data Tabulation Model (SDTM) and associated controlled terminology will be used. In cases of conflict, the Alzheimer's and COVID data standards will prevail. Towards stewardship of these standards, feedback will be provided to SDO where implementation challenges are encountered.
2. **Provide information systems and expert support for data and sample collection and management. ISAVRAD clinical data include medical history, SARS-CoV-2 infection, neurological and neuropsychological evaluations, neuroimaging, and biomarkers. Core 4** will support the digital infrastructure and management for 5 sites collecting data on Amerindians from the Andes mountains; Africans from Nigeria; and persons with variable admixture from Southern Texas (Mexican Americans); Seattle (non-tribal Native Americans); and the Bronx (Hispanic/Latinos and African Americans). All sites have agreed to share data and samples. Through accurate curation and data quality control and timely and complete description and reporting of data, **Core 4** will play a critical role in the collective study oversight by the **Core 1** (AC). **Core 4** will support secure, timely and user-friendly transfer of raw data from **Core 2** (CC) sites to **Core 3** (NIC); to and from NIA ADSP partners; and metadata from the Cores to the Projects and across Projects as needed to complete their aims and synergize collaborative efforts. **Core 4** will also be directly responsible for data sharing outside of the ISAVRAD consortium in accordance to the Data Sharing Plan and in close collaboration with the

leadership of **Core 1** (AC).

3. **Curate and prepare data for external sharing through national repositories. Core 4** supports data sharing by applying state-of-the-art standardized protocols for assessing dementia and providing rigorously collected, managed and documented data. *The efforts of the ISAVRAD study team will result in sharing DNA from understudied populations to NCRAD, whole genome sequence data to NIAGADS, and extensive clinical data and MRI images to NACC.* Our comprehensive data collection and handling documentation through the MOP, DMP and SAP and full traceability of all operations performed on data support reuse of shared data and reproducibility of this research.

CORE 3: Data Management & Statistics	Not Started	In Progress	Completed
Year 1 Deliverables			
Finalize REDCap data entry forms and processes			
Finalize QA expanded REDCap on-screen error checks for missing, out of range and inconsistent data to prevent, catch and correct errors as early as possible			
Finalize QA data integrity checks			
Establish a complete data inventory of enrollment, data and samples from all projects and cores is managed and maintained in REDCap			
Establish SOP to handle resolution of discrepancies identified through on-screen error checks are provided back to the local sites immediately through REDCap			
Establish and produce enrollment and data status reports to be run and made available daily, with standard reports including Planned versus Actual Enrollment by Site, Data Completeness Overall and by Site, Patient and Form, and Data Cleanliness Overall and by Site, Patient, Form, and for leadership and Project Officers, as well as work-level lists of the outstanding data and discrepancy.			
Establish an integrated clinical data from REDCap are written to the secure, cloud-based, inter-core analytics platform where it remains refreshed and available for project analysis.			
Integrate longitudinal omics, clinical and contextual (e.g., environmental) data to understand the impact of COVID-19 on progression to cognitive decline or ADRD.			
Develop target statistical learning analyses under the GLVM framework to assess a wide spectrum of predictors, including genetic and brain imaging biomarkers, clinical measures, and contextual factors to identify distinct/heterogeneous ADRD progression subtypes, the underlying factors and their interactions.			
Develop survival bias (or truncation due to death) in ADRD prediction			
Year 2 Deliverables			
Run QA expanded REDCap on-screen error checks for missing, out of range and inconsistent data to prevent, catch and correct errors as early as possible			
Run weekly QA data integrity checks			
Maintain a complete data inventory of enrollment, data and samples from all projects and cores is managed and maintained in REDCap			
Maintain SOP to handle resolution of discrepancies identified through on-screen error checks are provided back to the local sites immediately through REDCap			

Run daily enrollment and data status reports , with standard reports including Planned versus Actual Enrollment by Site, Data Completeness Overall and by Site, Patient and Form, and Data Cleanliness Overall and by Site, Patient, Form, and for leadership and Project Officers, as well as work-level lists of the outstanding data and Discrepancy (the multi-level nature of the reports provides a consistent study-level view samples and unresolved discrepancies that facilitate day-to-day management)			
Maintain an integrated clinical data from REDCap are written to the secure, cloud-based, inter-core analytics platform where it remains refreshed and available for project analysis.			
Integrate longitudinal omics, clinical and contextual (e.g., environmental) data to understand the impact of COVID-19 on progression to cognitive decline or ADRD.			
Conduct target statistical learning analyses under the GLVM framework to assess a wide spectrum of predictors, including genetic and brain imaging biomarkers, clinical measures, and contextual factors to identify distinct/heterogeneous ADRD progression subtypes, the underlying factors and their interactions.			
Conduct survival bias analyses (or truncation due to death) in ADRD prediction			
Year 3 Deliverables			
Run QA expanded REDCap on-screen error checks for missing, out of range and inconsistent data to prevent, catch and correct errors as early as possible			
Run weekly QA data integrity checks			
Maintain a complete data inventory of enrollment, data and samples from all projects and cores is managed and maintained in REDCap			
Maintain SOP to handle resolution of discrepancies identified through on-screen error checks are provided back to the local sites immediately through REDCap			
Run daily enrollment and data status reports , with standard reports including Planned versus Actual Enrollment by Site, Data Completeness Overall and by Site, Patient and Form, and Data Cleanliness Overall and by Site, Patient, Form, and for leadership and Project Officers, as well as work-level lists of the outstanding data and Discrepancy (the multi-level nature of the reports provides a consistent study-level view samples and unresolved discrepancies that facilitate day-to-day management)			
Maintain an integrated clinical data from REDCap are written to the secure, cloud-based, inter-core analytics platform where it remains refreshed and available for project analysis.			
Integrate longitudinal omics, clinical and contextual (e.g., environmental) data to understand the impact of COVID-19 on progression to cognitive decline or ADRD.			
Conduct target statistical learning analyses under the GLVM framework to assess a wide spectrum of predictors, including genetic and brain imaging biomarkers, clinical measures, and contextual factors to identify distinct/heterogeneous ADRD progression subtypes, the underlying factors and their interactions.			
Conduct survival bias analyses (or truncation due to death) in ADRD prediction			
Year 4 Deliverables			
Run QA expanded REDCap on-screen error checks for missing, out of range and inconsistent data to prevent, catch and correct errors as early as possible			
Run weekly QA data integrity checks			

Maintain a complete data inventory of enrollment, data and samples from all projects and cores is managed and maintained in REDCap			
Maintain SOP to handle resolution of discrepancies identified through on-screen error checks are provided back to the local sites immediately through REDCap			
Run daily enrollment and data status reports , with standard reports including Planned versus Actual Enrollment by Site, Data Completeness Overall and by Site, Patient and Form, and Data Cleanliness Overall and by Site, Patient, Form, and for leadership and Project Officers, as well as work-level lists of the outstanding data and Discrepancy (the multi-level nature of the reports provides a consistent study-level view samples and unresolved discrepancies that facilitate day-to-day management)			
Maintain an integrated clinical data from REDCap are written to the secure, cloud-based, inter-core analytics platform where it remains refreshed and available for project analysis.			
Integrate longitudinal omics, clinical and contextual (e.g., environmental) data to understand the impact of COVID-19 on progression to cognitive decline or ADRD.			
Conduct target statistical learning analyses under the GLVM framework to assess a wide spectrum of predictors, including genetic and brain imaging biomarkers, clinical measures, and contextual factors to identify distinct/heterogeneous ADRD progression subtypes, the underlying factors and their interactions.			
Conduct survival bias analyses (or truncation due to death) in ADRD prediction			
Year 5 Deliverables			
Run QA expanded REDCap on-screen error checks for missing, out of range and inconsistent data to prevent, catch and correct errors as early as possible			
Run weekly QA data integrity checks			
Maintain a complete data inventory of enrollment, data and samples from all projects and cores is managed and maintained in REDCap			
Maintain SOP to handle resolution of discrepancies identified through on-screen error checks are provided back to the local sites immediately through REDCap			
Run daily enrollment and data status reports , with standard reports including Planned versus Actual Enrollment by Site, Data Completeness Overall and by Site, Patient and Form, and Data Cleanliness Overall and by Site, Patient, Form, and for leadership and Project Officers, as well as work-level lists of the outstanding data and Discrepancy (the multi-level nature of the reports provides a consistent study-level view samples and unresolved discrepancies that facilitate day-to-day management)			
Maintain an integrated clinical data from REDCap are written to the secure, cloud-based, inter-core analytics platform where it remains refreshed and available for project analysis.			
Integrate longitudinal omics, clinical and contextual (e.g., environmental) data to understand the impact of COVID-19 on progression to cognitive decline or ADRD.			
Conduct target statistical learning analyses under the GLVM framework to assess a wide spectrum of predictors, including genetic and brain imaging biomarkers, clinical measures, and contextual factors to identify distinct/heterogeneous ADRD progression subtypes, the underlying factors and their interactions.			
Conduct survival bias analyses (or truncation due to death) in ADRD prediction			

Core 3 Year 1 Milestones

Milestone #1-1	**Finalize REDCap data entry forms and processes, QA expanded REDCap on-screen error checks, and data integrity checks**
Criteria for Success:	Complete REDCap forms, SOPs for data entry and QA.
Rationale:	Fast, accurate and complete data sets require sophisticated software and processes.
Progress:	*To be completed.*
Milestone #1-2	**Establish a complete data inventory of enrollment, data and samples from all projects and cores, and SOPs to handle resolution of discrepancies identified.**
Criteria for Success:	Complete data dictionaries and running inventories with working discrepancy resolution SOPs.
Rationale:	Data dictionaries and inventories are required for accurate interpretation of DNA sequencing results.
Progress:	*To be completed.*
Milestone #1-3	**Establish and produce weekly enrollment and data status (completeness, cleanliness, accuracy/discrepancy) reports by site for leadership and Project Officers, as well as transfer of integrated clinical data from REDCap to the secure, cloud-based, inter-core analytics platform where it remains refreshed and available for project analysis.**
Criteria for Success:	Accurate and complete weekly reports.
Rationale:	Accurate and fast reporting of data acquisition and quality is required for appropriate management and oversight of a project this size.
Progress:	*To be completed.*
Milestone #1-4	**Receive, track, and manage individual data from 1,434 individuals from wave 1 recruitment.**
Criteria for Success:	Accurate, complete and curated data from 1,434 individuals.
Rationale:	These data will eventually be added to the existing ADSP data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*
Milestone #1-5	**Integrate longitudinal omics, clinical and contextual (e.g., environmental) data to understand the impact of COVID-19 on progression to cognitive decline or ADRD; develop advanced statistical learning analyses to assess a wide spectrum of predictors, including genetic and brain imaging biomarkers, clinical measures, and contextual factors to identify distinct/heterogeneous ADRD progression subtypes, the underlying factors and their interactions; develop survival bias (or truncation due to death) in ADRD prediction.**
Criteria for Success:	Advanced statistical tools are available for individual projects in ISAVRAD.
Rationale:	Advanced statistical tools are required for the project aims.
Progress:	*To be completed.*

Year 1 Deliverables:

- **Complete, accurate and curated phenotype data for up to 1,433 participants.**
- **Assure that cleaned and quality-controlled data is deposited into NIAGADS**

Core 3 Year 2 Milestones

Milestone #2-1	**Receive, track, and manage individual data from up to new 1433 individuals from wave 2 recruitment and up to 716 follow up visits from wave 1**
Criteria for Success:	Accurate, complete and curated data from uo to 2,149 individuals.
Rationale:	These data will eventually be added to the existing ADSP data to provide additional power to examine both protective and risk effects.
Progress:	***To be completed.***
Milestone #2-2	**Receive, track, and manage whole genome sequencing data from samples transferred to NIAGADS and deposited in NCRAD by Core 1 for all newly collected Amerindian, African, African American and Hispanic samples from biospecimen samples from all collection sites.**
Criteria for Success:	Complete and curated WGS called data available for Project 2.
Rationale:	These data require storage and tracking for allocation for downstream applications.
Progress:	*To be completed.*
Milestone #2-3	**Tracking of samples for genotyping.**
Criteria for Success:	Up to 2,149 samples from Cores 1 and 4 are tracked in real time and reported accurately.
Rationale:	These materials will be transferred to the ADSP Genotyping Core facilities for downstream processing.
Progress:	*To be completed.*
Milestone #2-4	**Tracking and storage of results from genotyping, and quality control as performed at ADSP pipeline.**
Criteria for Success:	Genotyping data produced and QC'd according to existing ADSP pipelines for up to 2,149 samples is tracked and results from genotyping stored.
Rationale:	These data will eventually be added to the existing ADSP genotyping data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*
Milestone #2-5	**Plasma samples from all sites and transferred to Washington University School of Medicine for biobanking are accurately and timely tracked and results stored for up to 2,149 samples provided by Core 4**.
Criteria for Success:	Generation of plasma biomarker concentrations will be supported by a separate grant from Azlheimer's Association. Success will be achieved by accurate tracking and transfer of up to 2,149 samples.
Rationale:	Biomarker data on SARS-CoV-2 exposed older adults and controls is required for downstream Projects.
Progress:	*To be completed.*

Year 2 Deliverables:

- **Phenotype data stored for up to 2,149 participant visits**
- **DNA and plasma samples ascertained from US and internatonal sites are tracked and reported accurately.**
- **Genotyping data on up to 1,434 (1,000 Amerindian; 100 African; 334 US minority) individuals are managed and stored for downstream use and shared with ADSP for permanent storage**
- **Assure that cleaned and quality-controlled data is deposited into NIAGADS from GCAD**

Core 3 Year 3 Milestones	
Milestone #3-1	**Receive, track, and manage individual data from up to new 1433 individuals from wave 3 recruitment and up to 1,433 follow up visits from waves 1 and 2**
Criteria for Success:	Accurate, complete and curated data from uo to 2,866 individuals.
Rationale:	These data will eventually be added to the existing ADSP data to provide additional power to examine both protective and risk effects.
Progress:	***To be completed.***
Milestone #3-2	**Receive, track, and manage whole genome sequencing data from samples transferred to NIAGADS and deposited in NCRAD by Core 1 for all newly collected Amerindian, African, African American and Hispanic samples from biospecimen samples from all collection sites.**
Criteria for Success:	Complete and curated WGS called data available for Project 2.
Rationale:	These data require storage and tracking for allocation for downstream applications.
Progress:	*To be completed.*
Milestone #3-3	**Tracking of samples for genotyping.**
Criteria for Success:	Up to 4,300 samples from Cores 1 and 4 are tracked in real time and reported accurately.
Rationale:	These materials will be transferred to the ADSP Genotyping Core facilities for downstream processing.
Progress:	*To be completed.*
Milestone #3-4	**Tracking and storage of results from genotyping, and quality control as performed at ADSP pipeline.**
Criteria for Success:	Genotyping data produced and QC'd according to existing ADSP pipelines for up to 4,300 samples is tracked and results from genotyping stored.
Rationale:	These data will eventually be added to the existing ADSP genotyping data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*
Milestone #3-5	**Plasma samples from all sites and transferred to Washington University School of Medicine for biobanking are accurately and timely tracked and results stored for up to 4,300 individuals provided by Core 4.**
Criteria for Success:	Generation of plasma biomarker concentrations will be supported by a separate grant from Azlheimer's Association.

	Success will be achieved by accurate tracking and transfer of up to 4,300 individuals.
Rationale:	Biomarker data on SARS-CoV-2 exposed older adults and controls is required for downstream Projects.
Progress:	*To be completed.*

Year 3 Deliverables:

- **Phenotype data stored for up to 4,300 participants visit 1**
- **DNA and plasma samples ascertained from US and internatonal sites are tracked and reported accurately.**
- **Genotyping data on up to 4,300 (3,000 Amerindian; 300 African; 1,000 US minority) individuals (cummulative) are managed and stored for downstream use and shared with ADSP for permanent storage**
- **Assure that cleaned and quality-controlled data is deposited into NIAGADS from GCAD**

Core 3 Year 4 Milestones

Milestone #4-1	**Receive, track, and manage individual data from up to 2,149 follow up visits**
Criteria for Success:	Accurate, complete and curated data from uo to 2,149 individuals.
Rationale:	These data will eventually be added to the existing ADSP data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*
Milestone #4-2	**Receive, track, and manage whole genome sequencing data from samples transferred to NIAGADS and deposited in NCRAD by Core 1 for all newly collected Amerindian, African, African American and Hispanic samples from biospecimen samples from all collection sites.**
Criteria for Success:	Complete and curated WGS called data available for Project 2.
Rationale:	These data require storage and tracking for allocation for downstream applications.
Progress:	*To be completed.*
Milestone #4-3	**Tracking of samples for genotyping.**
Criteria for Success:	Up to 4,300 samples from Cores 1 and 4 are tracked in real time and reported accurately.
Rationale:	These materials will be transferred to the ADSP Genotyping Core facilities for downstream processing.
Progress:	*To be completed.*
Milestone #4-4	**Tracking and storage of results from genotyping, and quality control as performed at ADSP pipeline.**
Criteria for Success:	Genotyping data produced and QC'd according to existing ADSP pipelines for up to 2,149 samples is tracked and results from genotyping stored.
Rationale:	These data will eventually be added to the existing ADSP genotyping data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*

Milestone #4-5	**Plasma samples from all sites and transferred to Washington University School of Medicine for biobanking are accurately and timely tracked and results stored for up to 4,300 samples provided by Core 4.**
Criteria for Success:	Generation of plasma biomarker concentrations will be supported by a separate grant from Azlheimer's Association. Success will be achieved by accurate tracking and transfer of up to 4,300 individuals.
Rationale:	Biomarker data on SARS-CoV-2 exposed older adults and controls is required for downstream Projects.
Progress:	*To be completed.*

Year 4 Deliverables:

- **Phenotype data stored for up to 4,300 participant visits 1 and 2**
- **DNA and plasma samples ascertained from US and internatonal sites are tracked and reported accurately.**
- **Genotyping data on up to 4,300 (3,000 Amerindian; 300 African; 700 US minority) individuals are managed and stored for downstream use and shared with ADSP for permanent storage**
- **Assure that cleaned and quality-controlled data is deposited into NIAGADS from GCAD**

Core 3 Year 5 Milestones

Milestone #5-1	**Receive, track, and manage individual data from up to new 1433 follow up visits**
Criteria for Success:	Accurate, complete and curated data from uo to 4,300 individuals.
Rationale:	These data will eventually be added to the existing ADSP data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*
Milestone #5-2	**Receive, track, and manage whole genome sequencing data from samples transferred to NIAGADS and deposited in NCRAD by Core 1 for all newly collected Amerindian, African, African American and Hispanic samples from biospecimen samples from all collection sites..**
Criteria for Success:	Complete and curated WGS called data available for Project 2.
Rationale:	These data require storage and tracking for allocation for downstream applications.
Progress:	*To be completed.*
Milestone #5-3	**Tracking of samples for genotyping.**
Criteria for Success:	Up to 4,300 samples (cummulative) from Cores 1 and 4 are tracked in real time and reported accurately.
Rationale:	These materials will be transferred to the ADSP Genotyping Core facilities for downstream processing.
Progress:	*To be completed.*
Milestone #5-4	**Tracking and storage of results from genotyping, and quality control as performed at ADSP pipeline.**
Criteria for Success:	Genotyping data produced and QC'd according to existing

	ADSP pipelines for up to 4,300 samples (cummulative) are tracked and results from genotyping stored.
Rationale:	These data will eventually be added to the existing ADSP genotyping data to provide additional power to examine both protective and risk effects.
Progress:	*To be completed.*

Milestone #5-5	**Plasma samples from all sites and transferred to Washington University School of Medicine for biobanking are accurately and timely tracked and results stored for up to 2,149 samples provided by Core 4.**
Criteria for Success:	Generation of plasma biomarker concentrations will be supported by a separate grant from Azlheimer's Association. Success will be achieved by accurate tracking and transfer of up to 4,300 individuals (three visits each).
Rationale:	Biomarker data on SARS-CoV-2 exposed older adults and controls is required for downstream Projects.
Progress:	*To be completed.*

Year 5 Deliverables:

- **Phenotype data stored for up to 4,300 participants on 3 visits each**
- **DNA and plasma samples ascertained from US and internatonal sites are tracked and reported accurately.**
- **Genotyping data on up to 4,300 (3,000 Amerindian; 300 African; 700 US minority) individuals are managed and stored for downstream use and shared with ADSP for permanent storage**
- **Assure that cleaned and quality-controlled data is deposited into NIAGADS from GCAD**

Core 4 Milestones

MPIs	**Gabriel A. de Erausquin, MD, PhD, MSc Aleman PhD**	**Co-I**	**G. Gonzalez**
	Sudha Seshadri, MD		**Agustín Yécora, MD**
	Thomas Patterson, MD		**Rufus Akinyemi, MD**
	Mindy Katz, PhD		**Malveeka Sharma, MD**
			Mitzi Gonzalez, PhD

SPECIFIC AIMS: Core 4 (Clinical Core)

Core 4 will enroll and conduct in-depth clinical evaluations of 4,300 older adults with (75% of the sample) and without (25% of the sample) exposure to SARS-CoV-2 at baseline, and will conduct follow-up evaluations at 18 and 36 months. Clinical evaluations will include medical and epidemiological histories focused on SARS- CoV-2 infection, including COVID-19 case report forms (CRFs) harmonized by the WHO, neuropsychological assessment (including Uniform Data Set and a tablet-based, language-independent assessment), neurological examination, and completion of the semi-structured interview Schedules for Clinical Assessment in Neuropsychiatry of the World Health Organization (WHO SCAN), as well as informant report. At all data collection time-points, **Core 4** will also collect and ship blood biospecimens to carry out point-of-care COVID-19 antibody testing, extract DNA, and bank whole blood and plasma for future collaborative studies. It will also screen participants for MRI and harmonize MRI and PET data acquisition at all sites, sending imaging results to **Core 2** (NIC). **Core 4** will also

conduct case conferences to assign diagnostic clinical outcomes according to cognitive impairment level/ADRD status (unimpaired, mild cognitive impairment, dementia syndrome with disease-specific etiologies). Disease specific etiologies will include AD, Lewy-Body Dementia, Vascular Dementia, Frontal Lobe Dementia, and mixed. Finally, **Core 2** will employ a sophisticated data capture system, collaboratively developed with the Data Management and Statistics Core, to provide real- time data transmission to the ISAVRAD database via RedCAP. **Core 2** will be co-led by Dr. Gabriel A. de Erausquin Thomas Patterson, Dr. Sudha Seshadri, and Mindy Katz, with the assistance of site PIs Rufus Akinyemi (Nigeria), Agustin Yecora (Argentina) and Malveeka Sharma (Seattle). In addition to already having a strong working relationship, they have decades of experience in data collection from diverse and understudied cohorts, longitudinal data collection, and recruitment of persons with dementia.

Aim 1. Conduct evaluations of older adults post-exposure to SARS-CoV-2 at baseline (within one year
of recovery) and at 18 and 36 months follow-up visits according to standardized Core 4 protocols.

After informed consent and initial enrollment, baseline evaluations include detailed case report forms for COVID-19, neuropsychological assessment, semiquantitative neurological examination, semistructured behavioral neurology interviews, and additional relevant data. Provide follow-up examinations at 18 and 36 months for all participants using standardized assessments administered either at baseline. To ensure continuous reliability of data collection, oversee and conduct standardized training and periodic re-assessment in Core 2 procedures for clinicians.

Aim 2. Collect and Distribute, in coordination with Core 1, data and biosamples to the Projects and Cores, according to established criteria.

To support the mission of ADSP and Project 2, **Core 4** will obtain/distribute purified DNA for whole genome sequencing. Additional blood and plasma specimens will be biobanked for future use by a biomarkers project submitted separately to the Alzheimer's Association.
To support **Core 2** (NIC), **Core 2** will screen participants for MRI and PET acquisition, and harmonize acquisition of MRI data at all clinical sites.

Aim 3. Assign diagnostic clinical outcomes according to stage on the ADRD continuum annually for
each participant using an iterative process.

Assign a neurological impression of cognitive status based on the neurological evaluation.
Assign a neuropsychological impression of cognitive status based on the neuropsychological evaluation.
Assign a final consensus diagnosis of cognitively unimpaired, Mild Cognitive Impairment (MCI), or dementia syndrome with disease-specific etiologies including AD, Lewy-Body Dementia, Vascular Dementia, Frontal Lobe Dementia, and mixed dementia, by combining the neurological and neuropsychological impressions with results from behavioral, functional and informant assessments.

Aim 4. Collect and maintain longitudinal clinical, cognitive, and diagnostic outcomes data.

Core 4's data capture system, collaboratively developed with **Core 3** (DM&S), will provide real-time data transmission to the ISAVRAD database via RedCAP.

CORE 4: Clinical Core	Not Started	In Progress	Completed
Year 1 Deliverables			
Finalize sIRB consents and international site consents			
Finalize baseline Core 4 evaluation battery (including neuropsychological assessments, epidemiological and medical questionnaires, and screen for neuroimaging & FDG PET			
Finalize follow-up Core 4 evaluation battery			
Establish SOP for blood collection			
Train clinical personnel on clinical acquisition procedures and begin data collection			

Collect and transfer samples to NIAGAD, NCRAD & ADSP and to Washington University School of Medicine (Biomarker Core funded by Alzheimer's Association)			
To support Core 2 (NIC), Core 4 will screen participants for MRI and harmonize acquisition of MRI data at all clinical sites. For U.S. sites, the same will be done for PET scans.			
Finalize clinical data format on Redcap for tablet use			
Formulate and finalize tracking system			
Case conference diagnostic meetings			
Generate reports for IRB, NIH and the Alzheimer's Association			
Year 2 Deliverables			
Complete baseline Core 4 evaluation battery			
Transfer of Samples to Washington University School of Medicine (Biomarker Core supported by an Alzheimer's Association grant)			
Transfer of samples to NIAGAD, NCRAD & ADSP			
Case conference diagnostic meetings			
Create an annual training meeting for coordinators across sites			
Tear 3 Deliverables			
Begin follow-up Core 4 evaluations, specimen collection, screening for MRIs and FDG PET. and transfer of specimens.			
Case conference diagnostic meetings			
Continue an annual training meeting for coordinators across sites			
Manuscript preparation and scientific presentations			
Year 4 Deliverables			
Complete follow-up Core 2 evaluations, specimen collection, screening for f/u MRIs and FDG PET, and transfer of specimens			
Case conference diagnostic meetings			
Continue an annual training meeting for coordinators across sites			
Manuscript preparation and scientific presentations			
Year 5 Deliverables			
Compete outstanding follow-up Core 4 evaluations and specimen collections. And transfer of specimens.			
Manuscript preparation and scientific presentations			

Core 4 Year 1 Milestones

Milestone #4-1 **Y1 Finalize sIRB for sites within the U.S. and international site consents in coordination with the Core 1.**

Criteria for Success: Finalized culturally informed consent forms that are tailored to the sites and populations of interest that are agreed upon by the site PIs and investigative team.

Rationale: Culturally informed outreach consents are tailored to the populations of interest and the communities in which they live. These plans will improve our ability to enroll participants appropriately.

Progress: *Completed for Argentina, in progress for Nigeria*

Milestone #4-2 **Aim 1b: Y1 Finalize Core 4 evaluations which include: neuropsychological assessments, medical and epidemiological histories focused on SARS-CoV-2 infection, and a semi-structured neuropsychiatry assessment**

Criteria for Success: Finalized culturally informed outreach plans that are tailored to the respective sites and groups of interest in the participating countries/regions that are agreed upon by the site PIs and investigative team.

Rationale: Culturally informed outreach plans are tailored to the populations of interest and the communities in which they live. These plans will improve our ability to ascertain and enroll participants. Systematic capturing of data allows for pooling of data once standardization is achieved using local norms across sites. The battery was designed to adapt to multiple cultural settings and languages. It also allows for disseminating of data and collaborations with similar international studies.

Progress: *Completed for San Antonio, Laredo and Argentina. To be completed for Bronx, Seattle and Ibadan.*

Milestone #4-3 **Aim 1c: Y1 Finalize the follow-up Core 2 evaluation battery**

Criteria for Success: Finalized assessment protocols will be in place at US and international sites. These protocols will vary between the US and African sites but will contain shared instruments. All test materials will be reviewed by the US and international clinical leads and agreed upon.

Rationale: Shared assessment procedures using instruments that are common across sites will allow for reliable clinical data acquisition and support phenotypic harmonization of data.

Progress: *To be completed.*

Milestone #4-4 **Aim 1b and 1c: Y1 Train clinical personnel at US and international sites in all evaluation procedures and collect data at baseline.**

Criteria for Success: All clinical personnel at US and international sites will understand all aspects of the protocols and be able to collect and enter data in a systematic manner. Data collection will begin at baseline.

Rationale: Direct training in data collection and processing is key to acquiring uniform is critical to producing reliable clinical information.

Progress: *To be completed.*

Milestone #4-5 **Aim 2a: Y1 In coordination with the Administrative Core, establish SOP for blood collection.**

Criteria for Success: The proposed ISAVRAD is comprised of 5 clinical sites with uniform standard operating procedures for data collection, as well as uniform QC across sites and centralized oversight by Core 1 (AC). All methods were developed and harmonized through an expert consensus process over the course of the first several months of the pandemic, during the weekly Monday morning meetings of the Alzheimer's Association International Consortium on Chronic Neuropsychiatric Sequelae of SARS-CoV-2 4 (CNS-SC2), with additional meetings for specific topical subcommittees. Where necessary for harmonization of specific assessment tools or data acquisition methods, in person training will be coordinated by **Core 4** (CC) leadership at each site.

Rationale: Systematic collection of blood specimens will allow Clinical data collection using tablet-based administration will facilitate

standard data acquisition and ease of data management. Data elements need to be organized and presented in a standard format for use by the adjudication team.

Progress: *Completed.*

Milestone #1-6 **Aim 2a: Y1 In coordination with the Administrative Core, collect and ship biospecimens.**

Criteria for Success: **Core 4** sites will collect DNA for whole-genome sequencing in collabortion with the **Core 1** (AC) and the NIA Alzheimer's Disease Sequencing Project (ADSP), the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), and the Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). To support the external Biomarker Core at Washington University School of Medicine (funded by the Alzheimer's Association), **Core 4** will obtain and distribute blood and plasma specimens for use in standard clinical tests (e.g. inflammation, amyloid, tau and neurodegeneration, autophagy and genomic analysis).

Rationale: Clinical data collection using standard SOPs will facilitate Identifying genetic variations contributing to risk or resiliency of COVID-19 cognitive or neuropsychiatric sequelae, and its effect on longitudinal changes of blood-based biomarkers (BBB) in individuals with and without a history of COVID-19 infection. It will also enhance understanding of the effects of COVID-19 infection on AD-biomarkers, and to establish its interaction with the inflammatory response post-infection.

Progress: *To be completed.*

Milestone #4-7 **Aim 2b: Y1 To support Core 2 (NIC), Core 4 will screen participants for acquisition of MRI data at all clinical sites. For U.S. sites, the same will be done for FDG PET**

Criteria for Success: **Core 4** will screen and collaborate with Core 2 (NIC) to acquire MRI images and FDG PET (U.S. sites only).

Rationale: The clinical sites will screen participants during clinical data acquisition procedures to producing reliable clinical information across all sites.

Progress: *To be completed.*

Milestone #1-8 **Aim 3: Y1 Conduct case conferences to assign clinical diagnostic outcomes.**

Criteria for Success: Clinical consensus diagnoses for all initial and follow-up evaluations will be adjudicated at a monthly joint meeting.

Rationale: This project involves the collecting a large amount of clinical data in 4300 individuals across several sites. Uniform data capture is imperative across all data collection sites for this study to be successful.

Progress: *To be completed.*

Milestone #1-9 **Aim 4a: Y1 Create a data capture system in collaboration with Core 3 (DM&S).**

Criteria for Success: Create a real-time data entry system to capture data collection across for the respective sites with system checks and quality controls built in.

Rationale: Local and centralized diagnostic conferences will be conducted each week for all study participants at baseline and again at 24-

month follow-up. A continuous QC process will be conducted to ensure that diagnosis are consistent across sites.

Progress: *To be completed.*

Milestone #1-10 **Aim 4b: Y1 Create a tracking system to monitor ascertainment activities.**

Criteria for Success: Create a real-time tracking system in place to monitor ascertainment numbers for the respective sites and generate reports for the investigate team, the IRB, NIH, and the Alzheimer's Association.

Rationale: This project involves the recruitment of large numbers of individuals across several sites. Regular updates of progress toward ascertainment benchmarks will allow the Core D and study PIs to address ascertainment challenges as they arise. Reports to the IRB, and funding agencies (NIH and Alzheimer's Association) will be generated as well.

Progress: *To be completed.*

Year 1 Deliverables:

- **Finalize the clinical and neurocognitive assessment instruments and procedures**
- **Establish and finalize forms and questionnaires**
- **Finalize clinical data format on Redcap**
- **Train clinical personnel on clinical acquisition and sampling procedures**
- **Collect clinical and biological sample data**
- **Screen individuals for MRI and FDG PET**
- **Assign clinical diagnostic outcomes**
- **Successfully transfer samples to appropriate destinations**
- **Establish a tracking system to monitor ascertainment activities and generate reports for IRB, NIH, and the Alzheimer's Association**

Core 4 Year 2 Milestones

Milestone #4-1 **Aim 1b: Y2 Complete baseline Core 2 assessments and specimen collections.**

Criteria for Success: Clinical assessment and specimen collection for Y2 for US and international sites. Rationale: This study proposes to evaluate a total of 4,300 participants.

Progress: *To be completed.*

Milestone #4-2 **Aim 1b and 1c: Y2 Annual training meeting for coordinators across sites**

Criteria for Success: Progress will be monitored monthly to assure benchmarks are met and an annual training for coordinators will be hosted to assure consistency of assessments for US and international sites.

Rationale: Multiple sites have diverse geographic and population characteristics and may result in differences in evaluations or processing of samples.

Progress: *To be completed.*

Milestone #4-3 **Aim 2b: Y2 Screen individuals for MRI and FDG PET**

Criteria for Success: To support the aims of Core 2 (NIC).

Rationale: The clinical sites will screen participants during clinical data acquisition procedures to producing reliable clinical information across all sites.

Progress: *To be completed.*

Milestone #4-4	**Aim 3: Y2 Assign clinical diagnostic outcomes**
Criteria for Success:	Clinical consensus diagnoses for all initial and follow-up evaluations will be adjudicated at a monthly joint meeting.
Rationale:	This project involves the collecting a large amount of clinical data in 4300 individuals across several sites. Uniform data capture is imperative across all data collection sites for this study to be successful.
Progress:	*To be completed.*

Milestone #4-5	**Aim 2a: Y2 Transfer samples to appropriate destinations**
Criteria for Success:	Core 4 will continue to obtain and distribute blood and plasma specimens.
Rationale:	Specimens will be assayed for genetics, AD biomarkers, and inflammatory markers for those with and without a history of the COVID-19 infection.
Progress:	*To be completed.*

Milestone #4-2	**Aim 4b: Y2 Track progress.**
Criteria for Success:	Progress will be monitored monthly to assure benchmarks are met and an annual training for coordinators will be hosted to assure consistency of assessments for US and international sites.
Rationale:	Multiple sites have diverse geographic and population characteristics and may result in differences in evaluations or processing of samples.
Progress:	*To be completed.*

Year 2 Deliverables:

- **Collect clinical and biological samples**
- **Annual training meeting for coordinators**
- **Screen individuals for MRI and FDG PET**
- **Assign clinical diagnostic outcomes**
- **Successfully transfer samples to appropriate destinations**
- **Monitor the tracking system for ascertainment activities**

Core 4 Year 3 Milestones

Milestone #3-1	**Aim 1c: Y3 Begin follow-up Core 2 assessments and specimen collections.**
Criteria for Success:	Clinical assessment and specimen collection for Y3 for US and international sites. Rationale: This study proposes to evaluate follow-upon all active participants.
Progress:	*To be completed.*

Milestone #3-2	**Aim 2b: Y3 Screen follow-up participants for MRI and FDG PET**
Criteria for Success:	To support the aims of Core 3 (NIC) for follow-up evaluations.
Rationale:	The clinical sites will screen follow-up participants during clinical data acquisition procedures to producing reliable clinical information across all sites.
Progress:	*To be completed.*

Milestone #3-3	**Aim 2a: Y3 Transfer samples to appropriate destinations**
Criteria for Success:	Core 2 will continue to obtain and distribute blood and plasma

specimens.

Rationale: Specimens will be assayed for genetics, AD biomarkers, and inflammatory markers for those with and without a history of the COVID-19 infection.

Progress: *To be completed.*

Milestone #3-4 **Aim 3: Y3 Assign clinical diagnostic outcomes**

Criteria for Success: Clinical consensus diagnoses for all initial and follow-up evaluations will be adjudicated at a monthly joint meeting.

Rationale: Follow-up clinical diagnostic outcomes are crucial to achieving the Project aims. Uniform data capture is imperative across all data collection sites for this study to be successful.

Progress: *To be completed.*

Milestone #3-5 **Aim 1b and 1c: Y3 Annual training meeting for coordinators across sites**

Criteria for Success: Progress will be monitored monthly to assure benchmarks are met and an annual training for coordinators will be hosted to assure consistency of assessments for US and international sites.

Rationale: Multiple sites have diverse geographic and population characteristics and may result in differences in evaluations or processing of samples.

Progress: *To be completed.*

Milestone #3-6 **Aim 4b: Y3 Track progress, produce scientific manuscripts and presentations, and report to the IRB and funding agencies.**

Criteria for Success: Progress will be monitored monthly to assure benchmarks are met, dissemination of scientific results are accomplished, and reports to governing agencies are produced.

Rationale: Oversight and reporting are necessary to accomplish the aims of this Core and the Overall components of the U19.

Progress: *To be completed.*

Year 3 Deliverables:

- **Collect follow-up clinical evaluations and biological samples**
- **Screen follow-up participants for MRI and FDG PET**
- **Successfully transfer samples to appropriate destinations**
- **Assign clinical diagnostic outcomes**
- **Annual training meeting for coordinators**
- **Monitor the tracking system for ascertainment activities, produce scientific and governing agency reports**

Core 4 Year 4 Milestones

Milestone #4-1 **Aim 1c: Y4 Continue follow-up Core 2 assessments and specimen collections.**

Criteria for Success: Clinical assessment and specimen collection for Y4 for US and international sites.

Rationale: This study proposes to evaluate follow-upon all active participants.

Progress: *To be completed.*

Milestone #4-2 **Aim 2b: Y4 Screen follow-up participants for MRI and FDG PET**

Criteria for Success:	To support the aims of Core 3 (NIC) for follow-up evaluations.
Rationale:	The clinical sites will screen follow-up participants during clinical data acquisition procedures to producing reliable clinical information across all sites.
Progress:	*To be completed.*

Milestone #4-3	**Aim 2a: Y4 Transfer samples to appropriate destinations**
Criteria for Success:	Core 2 will continue to obtain and distribute blood and plasma specimens.
Rationale:	Specimens will be assayed for genetics, AD biomarkers, and inflammatory markers for those with and without a history of the COVID-19 infection.
Progress:	*To be completed.*
Milestone #4-4	**Aim 3: Y4 Assign clinical diagnostic outcomes**
Criteria for Success:	Clinical consensus diagnoses for all initial and follow-up evaluations will be adjudicated at a monthly joint meeting.
Rationale:	Follow-up clinical diagnostic outcomes are crucial to achieving the Project aims. Uniform data capture is imperative across all data collection sites for this study to be successful.
Progress:	*To be completed.*

Milestone #4-5	**Aim 1b and 1c: Y4 Annual training meeting for coordinators across sites**
Criteria for Success:	Progress will be monitored monthly to assure benchmarks are met and an annual training for coordinators will be hosted to assure consistency of assessments for US and international sites.
Rationale:	Multiple sites have diverse geographic and population characteristics and may result in differences in evaluations or processing of samples.

Milestone #4-6	**Aim 4b: Y4 Track progress, produce scientific manuscripts and presentations, and report to the IRB and funding agencies.**
Criteria for Success:	Progress will be monitored monthly to assure benchmarks are met, dissemination of scientific results are accomplished, and reports to governing agencies are produced.
Rationale:	Oversight and reporting are necessary to accomplish the aims of this Core and the Overall components of the U19.
Progress:	*To be completed.*

Year 4 Deliverables:

- **Collect follow-up clinical evaluations and biological samples**
- **Screen follow-up participants for MRI and FDG PET**
- **Successfully transfer samples to appropriate destinations**
- **Assign clinical diagnostic outcomes**
- **Annual training meeting for coordinators**
- **Monitor the tracking system for ascertainment activities, produce scientific and governing agency reports**

Core 4 Year 5 Milestones

Milestone #5-1	**Aim 1c: Y5 Complete outstanding follow-up Core 2 assessments and specimen collections and final transfer of specimens.**

Criteria for Success:	Clinical assessment and specimen collection for outstanding follow-ups for US and international sites.
Rationale:	This study proposes to evaluate follow-upon all active participants.
Progress:	*To be completed.*

Milestone #5-2	**Aim 4b: Y5 Analyses, manuscript preparation and scientific presentations**
Criteria for Success:	Dissemination of data and results to the scientific community and share summary data on various data platforms for investigators to gain access
Rationale:	Complete analyses of the collected data and share results with the scientific community.
Progress:	*To be completed.*

Year 5 Deliverables

- **Complete outstanding follow-up CC assessments, specimen collection, and final transfer of specimens.**
- **Accepted manuscripts to peer-reviewed scientific journals and presentation of results at scientific meetings**

Project 1 Milestones

MPIs: Gabriel A. de Erausquin, MD, PhD (Contact) **Co-I Chen-Pin Wang, PhD**

Jorge Zwir, PhD

Specific Aims. Project 1 (Longitudinal Epidemiology of Cognitive Decline and Alzheimer's Dementia after SARS-CoV-2 Infection).

Project 1 of ISAVRAD will describe the longitudinal course, epidemiological risk/resiliency factors, and environmental interactions predictive of cognitive decline and progress to ADRD following SARS-CoV-2 infection in older adults from ancestral and admixed populations. We propose the following specific aims:

Aim 1. Longitudinally compare the rate of cognitive decline in older adults with and without exposure to SARS-CoV-2 infection. We hypothesize that these changes are progressive in nature and that, over the 3-year follow-up of the proposed study, will increase rates of ADRD based on Clinical Dementia Rating scores and neurocognitive performance.

Aim 2. For the infected group, compare outcomes by severity of COVID-19 symptoms and the presence and severity of anosmia. We will stratify by severity of COVID-19 symptoms using the WHO guidelines, the level of care required during the acute phase of the illness (e.g., none, minimal, ambulatory care, hospital admission, ICU/mechanical ventilation), and by presence and severity of anosmia. We hypothesize that hyposmia/anosmia, but not the severity of COVID-19 during the acute phase, predicts the presence and likelihood of progression of cognitive impairment and ADRD.

Aim 3. Identify predictors of SARS-CoV-2-induced cognitive decline. Interacting with Core 2 (NIC) and Project 2, we will use precision medicine strategies based on deep-learning to uncover multidimensional (feature-based) predictors of SARS-CoV-2 induced decline in individual cognitive domains/profiles. We hypothesize that specific symptoms (anosmia-hyposmia) will segregate with related neuroimaging changes (in the olfactory cortical network) and abnormalities in peripheral markers of Alzheimer's disease, will predict with the highest risk of cognitive decline and new onset ADRD.

Project 1 Year 1 Milestones

Milestone #1-1	**Aim 1. Establish data access routes.** In coordination with the Cores, we will develop operating procedures for transferring data for analysis.
Criteria for Success:	Successful access to Year 1 cohort data resources.
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #1-2	**Aim 1. Obtain and perform preliminary analysis of ~1.000 Argentinian Amerindians.**
Criteria for Success:	Successful access to Aim 1 preliminary phenotype data and analysis. In coordination with Core 4, we will collect all relevant Year 1 data for preliminary baseline analyses of ADRD-related endophenotypes including baseline neurocognitive measures, neuroimaging measures, and infection information, and covariates.
Rationale:	Provide phenotype variation characterization of the previously unstudied Argentinian Amerindian cohort.
Progress:	*To be completed.*
Milestone #1-3	**Aim 1. Establish pipeline for disease (COVID-19) environment**

	kernels (Core 4), neuroimaging signatures (Project 3) and ancestry genetic markers (from Project 2). We will implement a pipeline for disease environment kernel matrix estimation that will utilize various measures of neurological symptoms and severity of COVID-19 infection.
Criteria for Success:	Successful implement of infection environment kernel estimation.
Rationale:	Derived infection environment similarity matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*

Milestone #1-4	**Aim 2. Establish pipeline for longitudinal explanatory AI data analysis.**
Criteria for Success:	Successful implementation of explanatory AI methodology.
Rationale:	Longitudinal analysis of complex multidimensional data will require xAI methods.
Progress:	*To be completed.*

Project 1 Year 1 Deliverables:

- **Create and test data access and transfer routes from generating Cores and Projects.**
- **Perform preliminary characterization of Argentinian Amerindian phenotype variation in Year 1 samples.**
- **Implement pipeline for data transfer from Core 4, Project 2 and Project 3**
- **Implement a pipeline for explanatory AI multidimensional longitudinal analysis of COVID-19 data**

Project 1 Year 2 Milestones

Milestone #2-1	**Aim 1. Update data sources.** In coordination with the Cores, we will update data for analysis.
Criteria for Success:	Successful access to Year 1 and 2 cohort data resources.
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*

Milestone #2-2	**Aim 1. Obtain and perform preliminary analysis of ~2.200 Amerindians, ~200 Africans and ~750 admixed Hispanics and African Americans**
Criteria for Success:	Successful access to phenotype data and analysis. In coordination with Core 4, we will collect all relevant Year 1 data for preliminary baseline analyses of ADRD-related endophenotypes including baseline neurocognitive measures, neuroimaging measures, and infection information, and covariates.
Rationale:	Provide phenotype variation characterization of the previously unstudied Argentinian Amerindian cohort.
Progress:	*To be completed.*

Milestone #2-3	**Aim 1. Update disease (COVID-19) environment kernels (Core 4), neuroimaging signatures (Project 3) and ancestry genetic markers (from Project 2).** We will update data for disease environment kernel matrix estimation that will utilize various measures of neurological symptoms and severity of COVID-19 infection.
Criteria for Success:	Successful implement of infection environment kernel estimation.
Rationale:	Derived infection environment similarity matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*

Milestone #2-4	**Aim 2. Test pipeline for longitudinal explanatory AI data analysis.**
Criteria for Success:	Successful testing of explanatory AI methodology on preliminary data from Core 4, Project 2 and Project 3.
Rationale:	Longitudinal analysis of complex multidimensional data will require xAI methods.
Progress:	*To be completed.*

Project 1 Year 2 Deliverables:

- **Update data transfers from generating Cores and Projects for 65% of the cohort.**
- **Update data from Core 4, Project 2 and Project 3**
- **Perform characterization of Amerindian, African, and Admixed Hispanic and African American long-COVID-19 phenotype variation in Year 1-2 samples (65% of the cohort).**
- **Test explanatory AI multidimensional longitudinal analysis of COVID-19 data**

Project 1 Year 3 Milestones

Milestone #3-1	**Aim 1. Update data sources.** In coordination with the Cores, we will update data for analysis.
Criteria for Success:	Successful access to Year 1-2 cohort data resources.
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*

Milestone #3-2	**Aim 1. Obtain and perform preliminary analysis of ~3,000, ~300 Africans and ~1,000 admixed Hispanics and African Americans**.
Criteria for Success:	Successful access to phenotype data and analysis. In coordination with Core 4, we will collect all relevant Year 1-2 data for preliminary baseline analyses of ADRD-related endophenotypes including baseline neurocognitive measures, neuroimaging measures, and infection information, and covariates.
Rationale:	Provide phenotype variation characterization of the previously unstudied Argentinian Amerindian cohort.
Progress:	*To be completed.*

Milestone #3-3	**Aim 1. Update disease (COVID-19) environment kernels (Core 4), neuroimaging signatures (Project 3) and ancestry genetic markers (from Project 2).** We will update data for disease environment kernel matrix estimation that will utilize various measures of neurological symptoms and severity of COVID-19 infection.
Criteria for Success:	Successful implement of infection environment kernel estimation.
Rationale:	Derived infection environment similarity matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*

Milestone #3-4	**Aim 2. Test pipeline for longitudinal explanatory AI data analysis.**
Criteria for Success:	Successful testing of explanatory AI methodology on preliminary data from Core 4, Project 2 and Project 3.
Rationale:	Longitudinal analysis of complex multidimensional data will require xAI methods.
Progress:	*To be completed.*

Project 1 Year 3 Deliverables:

- **Update data transfers from generating Cores and Projects for 100% of the cohort initial assessments.**

- **Update data from Core 4, Project 2 and Project 3**
- **Perform characterization of Amerindian, African, and Admixed Hispanic and African American long-COVID-19 phenotype variation in Year 1-2 samples (100% of the cohort) and preliminary analysis of follow up data (65 % of wave 2).**
- **Preliminary explanatory AI multidimensional longitudinal analysis of COVID-19 data**

Project 1 Year 4 Milestones

Milestone #4-1	**Aim 1. Update data sources.** In coordination with the Cores, we will update data for analysis.
Criteria for Success:	Successful access to Year 1 -3 cohort data resources.
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #4-2	**Aim 1. Obtain and perform preliminary analysis of visits 1 and 2 in ~3,000, ~300 Africans and ~1,000 admixed Hispanics and African Americans**.
Criteria for Success:	Successful access to phenotype data and analysis. In coordination with Core 4, we will collect all relevant Year 1-3 for preliminary baseline analyses of ADRD-related endophenotypes including baseline neurocognitive measures, neuroimaging measures, and infection information, and covariates.
Rationale:	Provide phenotype variation characterization of the previously unstudied Argentinian Amerindian cohort.
Progress:	*To be completed.*
Milestone #4-3	**Aim 1. Update disease (COVID-19) environment kernels (Core 4), neuroimaging signatures (Project 3) and ancestry genetic markers (from Project 2).** We will update data for disease environment kernel matrix estimation that will utilize various measures of neurological symptoms and severity of COVID-19 infection.
Criteria for Success:	Successful implement of infection environment kernel estimation.
Rationale:	Derived infection environment similarity matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*
Milestone #4-4	**Aim 2. Carry out preliminary longitudinal explanatory AI data analysis on visits 1 and 2.**
Criteria for Success:	Successful testing of explanatory AI methodology on preliminary data from Core 4, Project 2 and Project 3.
Rationale:	Longitudinal analysis of complex multidimensional data will require xAI methods.
Progress:	*To be completed.*

Project 1 Year 4 Deliverables:

- **Update data transfers from generating Cores and Projects for 100% of the cohort initial assessments and 100% of visit 2 data.**
- **Update data from Core 4, Project 2 and Project 3**
- **Perform characterization of Amerindian, African, and Admixed Hispanic and African American long-COVID-19 phenotype variation in Year 1-2 samples (100% of the cohort) and preliminary analysis of follow up data (100 % of wave 2).**
- **Preliminary explanatory AI multidimensional longitudinal analysis of COVID-19 data**

Project 1 Year 5 Milestones

Milestone #5-1	**Aim 1. Update data sources.** In coordination with the Cores, we will update data for analysis.
Criteria for Success:	Successful access to Year 1-4 cohort data resources.
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #5-2	**Aim 1. Carry out complete analysis of visits 1, 2 and 3 in ~3,000, ~300 Africans and ~1,000 admixed Hispanics and African Americans**.
Criteria for Success:	Successful access to phenotype data and analysis. In coordination with Core 4, we will collect all relevant Year 1-5 data for analyses of ADRD-related endophenotypes including baseline neurocognitive measures, neuroimaging measures, and infection information, and covariates.
Rationale:	Provide phenotype variation characterization of the previously unstudied Argentinian Amerindian cohort.
Progress:	*To be completed.*
Milestone #5-3	**Aim 1. Update disease (COVID-19) environment kernels (Core 4), neuroimaging signatures (Project 3) and ancestry genetic markers (from Project 2).** We will update data for disease environment kernel matrix estimation that will utilize various measures of neurological symptoms and severity of COVID-19 infection.
Criteria for Success:	Successful implement of infection environment kernel estimation.
Rationale:	Derived infection environment similarity matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*
Milestone #5-4	**Aim 2. Carry out preliminary longitudinal explanatory AI data analysis on visits 1 and 2.**
Criteria for Success:	Successful testing of explanatory AI methodology on preliminary data from Core 4, Project 2 and Project 3.
Rationale:	Longitudinal analysis of complex multidimensional data will require xAI methods.
Progress:	*To be completed.*

Project 1 Year 5 Deliverables:

- **Update data transfers from generating Cores and Projects for 100% of the cohort initial assessments and 100% of visits 2 and 3 data.**
- **Update data from Core 4, Project 2 and Project 3**
- **Perform characterization of Amerindian, African, and Admixed Hispanic and African American long-COVID-19 phenotype variation in Year 1-3 samples (100% of the cohort) and analysis of follow up data (100 % of waves 2 and 3).**
- **Final explanatory AI multidimensional longitudinal analysis to establish predictors COVID-19-induced cognitive change data including neuroimaging signature-, ancestry marker- and plasma biomarker-based predictors**

Project 2 Milestones

MPIs: John Blangero, PhD (Contact)
Sarah Williams-Blangero, PhD
Almeida PhD

Co-I **Vincent Diego PhD**
Marcio AA

Gladys Maestre PhD

SPECIFIC AIMS: Project 2 (Gene×Environment Interactions on Risk of Cognitive Decline after SARS-CoV-2 Infection)

Aim 1. Detect Genetic Influences on Endophenotypic Responses to COVID-19 Infection. Using WGS data, we will estimate the overall heritability of ADRD-relevant phenotypic response to infection in the two larger cohorts (Amerindians and Mexican Americans). A significant heritability is a formal test of a genotype×infection interaction hypothesis. Phenotypes include three-year changes in neurocognitive measures, neuroimaging measures, and blood-based biomarkers of AD-related pathology, neurodegeneration, and neuronal damage.

Aim 2. Test Sequence Variation in Genes and Gene Pathways Influencing Response to COVID-19. Using a variety of statistical genetic methods, we will initially search for evidence that variation at the gene level differentially (i.e., showing different magnitudes of effects in cases versus controls) influences response. We also will perform genome-wide gene- and pathway-based association searches focused separately on protein altering variation (weighted using functional prediction) and regulatory variation (using imputed genetic values of gene expression). Joint tests across all populations will be performed allowing for between-population heterogeneity in the genetic basis of response to infection.

Aim 3. Genetics of Between-Population Variation in Mean Responses to Infection. Just as individuals differ in response, we anticipate population differences in response. Using a hierarchical mixed model and between-population estimates of expected identity-by-descent (or identity-by-state) genetic covariances derived from allele frequency differences, we will formally test ADRD-related phenotypes for a genetic component influencing observed between-population differences in response to COVID-19 infection.

Project 2 Year 1 Milestones

Milestone #1-1 **Aim 1. Establish data access routes.** In coordination with the Cores, we will develop operating procedures for transferring data for analysis.
Criteria for Success: Successful access to Year 1 cohort data resources.
Rationale: Data needed for analyses of Aims 1-3.
Progress: *To be completed.*

Milestone #1-2 **Aim 1. Obtain and perform preliminary analysis of ~400 Argentinian Amerindians WGS.** Compressed CRAM files and called VCF files will be transferred from the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS). Since this Amerindian population has not been previously characterized for WGS variation, we will make an initial assessment on ~400 WGS samples that will be available from a pilot study within the first quarter of funding
Criteria for Success: Successful access to Aim 1 preliminary sequence data and analysis.
Rationale: Provide genetic variation characterization of the previously unstudied Argentinian Amerindian cohort.
Progress: *To be completed.*

Milestone #1-3 **Aim 1. Obtain all Year 1 baseline ADRD-related endophenotype,**

	WGS, infection and covariate data. In coordination with the Cores, we will collect all relevant Year 1 data for preliminary baseline analyses of ADRD-related endophenotypes including baseline neurocognitive measures, neuroimaging measures, and blood-blased biomarkers, infection information, and covariates.
Criteria for Success:	Successful transfer and validation of Year 1 cohort data resources.
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #1-4	**Aim 1. Establish pipeline for empirical relatedness calculation and ancestry estimation.** We will implement a robust pipeline for empirical relatedness calculation and individual-specific ancestry estimates. We will trial these with Year 1 data.
Criteria for Success:	Successful implementation of relatedness and ancestry estimation procedures.
Rationale:	Derived genetic measures are needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #1-5	**Aim 1. Establish pipeline for disease (COVID-19) environment kernels.** We will implement a pipeline for disease environment kernel matrix estimation that will utilize various measures of neurological symptoms and severity of COVID-19 infection.
Criteria for Success:	Successful implementation of infection environment kernel estimation.
Rationale:	Derived infection environment similarity matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*
Milestone #1-6	**Aim 1. Establish pipeline for estimation of whole genome polygenic values (WGPVs).** We will implement a pipeline for estimation of endophenotypic whole genome polygenic values using BLUP.
Criteria for Success:	Successful implementation of WGPV BLUP estimation procedure.
Rationale:	Derived WGPVs are needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #1-7	**Aim 2. Establish pipeline for identification and weighting of protein altering and regulatory variation.** We will implement a robust functional annotation process to utilize all known relevant bioinformatic information. We will place variants into aggregates of genes and gene pathways.
Criteria for Success:	Successful annotation of Year 1 WGS data and aggregation into genes and gene pathways.
Rationale:	Derived gene and pathway sets are needed for analyses of Aim 2.
Progress:	*To be completed.*
Milestone #1-8	**Aim 2. Establish pipeline for gene and gene pathway kernel estimation.** We will implement a pipeline for gene and pathway kernel estimation using both protein altering variants and putative regulatory variants.
Criteria for Success:	Successful implementation of gene and gene pathway kernel estimation procedures using general protein distance approaches and IBD approaches.
Rationale:	Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.
Progress:	*To be completed.*

Project 2 Year 1 Deliverables:

- **Create and test data access and transfer routes from generating Cores.**
- **Perform preliminary characterization of Argentinian Amerindian sequence variation in Year 1 samples.**
- **Update all existing relevant data for Project 2.**
- **Implement pipeline for empirical relatedness calculation and ancestry calculation; perform analyses on existing Year 1 data**
- **Implement a pipeline for disease (COVID-19) environment kernels.**
- **Implement a pipeline of WPGV estimation.**
- **Implement pipeline for functional annotation and develop variant sets for genes and gene pathways.**
- **Implement a pipeline for gene-specific and pathway-specific sequence variation kernels.**

Project 2 Year 2 Milestones

Milestone #2-1	**Aim 1. Update ADRD-related endophenotype, WGS, infection and covariate information with Year 2 data.** In coordination with the Cores, we will collect all relevant Year 2 data and update the total data set.
Criteria for Success:	Successful transfer and validation of Year 2 cohort data resources and incorporation with prior data.
Rationale:	Data needed for updated analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #2-2	**Aim 1. Obtain empirical relatedness calculation and ancestry estimates.** Using all available data, we will calculate and store within-population empirical genetic relatedness matrices and within-population ancestry estimates.
Criteria for Success:	Successful calculation of relatedness and ancestry estimates incorporating data from Years 1-2.
Rationale:	Derived genetic measures are needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #2-3	**Aim 1. Obtain disease environment kernel matrix.** Using all available data, we will calculate and store within-population disease environment kernel matrices
Criteria for Success:	Successful calculation of relatedness and ancestry estimates incorporating data from Years 1-2.
Rationale:	Derived genetic measures are needed for analyses of Aim 1.
Progress:	*To be completed.*
Milestone #2-4	**Aim 1. Preliminary quantitative genetic analysis of baseline cross-sectional data from Years 1-2.** Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of heritability for each baseline ADRD-related endophenotype and genetic correlations between endophenotypes. We will also perform initial cross-sectional tests of genotype-by-infection interactions (GEI).
Criteria for Success:	Successful preliminary estimation of heritability of baseline ADRD-endophenotypes, genetic correlations between endophenotypes, and GEI.
Rationale:	Establish heritability of focal ADRD-related endophenotypes at baseline and cross-sectional evidence of GEI.
Progress:	*To be completed.*

Milestone #2-5	**Aim 1. Obtain polygenic value estimation.** We will estimate WPGVs for each subject for each ADRD-related endophenotype using the mixed model BLUP approach.
Criteria for Success:	Successful generation of Year 1-2 WPGVs.
Rationale:	Derived WGPVs are needed for analyses of Aim 1-3.
Progress:	*To be completed.*

Milestone #2-6	**Aim 2. Update identification and weighting of protein altering and regulatory variation.** As new data accumulate, we will identify new sequence variants that were not previously detected, functionally annotate them, and incorporate into gene and gene pathway set.
Criteria for Success:	Successful updating of WGS data and aggregation into genes and gene pathways using data from Years 1-2.
Rationale:	Derived gene and pathway sets are needed for analyses of Aim 2.
Progress:	*To be completed.*

Milestone #2-7	**Aim 2. Obtain gene and gene pathway kernel matrix estimates.** Using all available Year 1-2 data, we will estimate and store gene and pathway kernel matrix estimates using both protein altering variants and putative regulatory variants.
Criteria for Success:	Successful calculation of gene and pathway kernel matrix estimates incorporating data from Years 1-2.
Rationale:	Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.
Progress:	*To be completed.*

Project 2 Year 2 Deliverables:

- **Update all existing relevant data for Project 2.**
- **Generate empirical relatedness estimates and ancestry estimates for data from Year 1-2.**
- **Generate disease (COVID-19) environment kernels estimates.**
- **Obtain preliminary estimates of baseline endophenotype within-population heritability and initial tests of cross-sectional GEI.**
- **Generate estimates of WPGVs for each baseline ADRD-endophenotype.**
- **Update functional annotation and develop variant sets for genes and gene pathways using combined data from Years 1-2.**
- **Generate gene-specific and pathway-specific sequence variation kernels.**

Project 2 Year 3 Milestones

Milestone #3-1	**Aim 1. Update ADRD-related endophenotype, WGS, infection and covariate information with Year 3 data.** In coordination with the Cores, we will collect all relevant Year 3 data and update the total data set.
Criteria for Success:	Successful transfer and validation of Year 3 cohort data resources and incorporation with prior data.
Rationale:	Data needed for updated analyses of Aims 1-3.
Progress:	*To be completed.*

Milestone #3-2	**Aim 1. Update empirical relatedness calculation and ancestry estimates.** Using all available data, we will update and store within-population empirical genetic relatedness matrices and within-population ancestry estimates.
Criteria for Success:	Successful update of relatedness and ancestry estimates incorporating

	data from Years 1-3..
Rationale:	Derived genetic measures are needed for analyses of Aim 1-3.
Progress:	*To be completed.*
Milestone #3-3	**Aim 1. Update disease environment kernel matrix.** Using all available data, we will calculate and store within-population disease environment kernel matrices
Criteria for Success:	Successful calculation of relatedness and ancestry estimates incorporating data from Years 1-3.
Rationale:	Derived genetic measures are needed for analyses of Aim 1.
Progress:	*To be completed.*
Milestone #3-4	**Aim 1. Preliminary quantitative genetic analysis of baseline cross-sectional data and longitudinal data from Years 1-3.** Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of heritability for each baseline ADRD-related endophenotype and genetic correlations between endophenotypes. We will also perform cross-sectional and longitudinal (using endophenotypic responses between baseline and 18-month examinations) tests of genotype-by-infection interactions (GEI).
Criteria for Success:	Successful preliminary estimation of heritability of baseline ADRD-endophenotypes, genetic correlations between endophenotypes, and both cross-sectional and longitudinal tests of GEI.
Rationale:	Establish heritability of focal ADRD-related endophenotypes at baseline and cross-sectional and longitudinal evidence of GEI.
Progress:	*To be completed.*
Milestone #3-5	**Aim 1. Update polygenic value estimation and perform GEI tests using WPGVs.** Using all available Year 1-3 data, we will update estimates of WPGVs for each subject for each ADRD-related endophenotype using the mixed model BLUP approach. We will use these in tests of GEI.
Criteria for Success:	Successful generation of Year 1-3 WPGVs and WPGV-based tests of GEI.
Rationale:	Derived WGPVs are needed for analyses of Aim 1-3.
Progress:	*To be completed.*
Milestone #3-6	**Aim 1. Establish pipeline for spatial distance kernels and obtain estimates of distance matrix using geocode information.** We will implement a pipeline for estimating spatial distances from geocode information and calculate the spatial distance between all available within-population subjects.
Criteria for Success:	Successful implement of spatial distance calculation and calculation for all Year 1-3. data.
Rationale:	Spatial distance matrices are needed for analyses of Aim 1.
Progress:	*To be completed.*
Milestone #3-7	**Aim 1. Preliminary spatial analysis of baseline cross-sectional data and longitudinal data from Years 1-3.** Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of the importance of environmentally determined spatial variation for each baseline ADRD-related endophenotype and longitudinal endophenotypic response measures (using baseline and 18-month examinations).
Criteria for Success:	Successful preliminary estimation of spatial components of baseline

	ADRD-endophenotypes and 18-month endophenotypic response measures.
Rationale:	Establish environmental spatial influences on ADRD-related endophenotypes.
Progress:	*To be completed.*

Milestone #3-8	**Aim 2. Update identification and weighting of protein altering and regulatory variation.** As new data accumulate, we will identify new sequence variants that were not previously detected, functionally annotate them, and incorporate into gene and gene pathway set.
Criteria for Success:	Successful updating of WGS data and aggregation into genes and gene pathways using data from Years 1-3.
Rationale:	Derived gene and pathway sets are needed for analyses of Aim 2.
Progress:	*To be completed.*

Milestone #3-9	**Aim 2. Update gene and gene pathway kernel matrix estimates and perform initial gene/gene pathway tests on ADRD-endophenotypes and GEI.** Using all available Year 1-3 data, we will estimate and store gene and pathway kernel matrix estimates using both protein altering variants and putative regulatory variants. We will also use these to test for gene and/or gene pathway specific influences on endophenotypes and their response.
Criteria for Success:	Successful calculation of gene and pathway kernel matrix estimates and initial test of their effects incorporating data from Years 1-3.
Rationale:	Identification of specific genes and/or gene pathways playing a role in GEI are the focus of Aim 2.
Progress:	*To be completed.*

Project 2 Year 3 Deliverables:

- **Update all existing relevant data for Project 2.**
- **Update empirical relatedness estimates and ancestry estimates using data from Years 1-3.**
- **Update disease (COVID-19) environment kernels estimates using data from Years 1-3.**
- **Obtain preliminary estimates of baseline endophenotype within-population heritability and initial tests of cross-sectional and longitudinal GEI using data from Years 1-3.**
- **Update estimates of WPGVs for each baseline ADRD-endophenotypes and use them in tests of GEI for data from Years 1-3.**
- **Generate spatial distance matrices for data from Years 1-3.**
- **Obtain preliminary estimates of baseline endophenotype within-population spatial components of variability in joint models with genetic factors using data from Years 1-3.**
- **Update functional annotation and develop variant sets for genes and gene pathways using combined data from Years 1-3.**
- **Update gene-specific and pathway-specific sequence variation kernels and perform initial tests using data from Years 1-3.**

Project 2 Year 4 Milestones

Milestone #4-1	**Aim 1. Update ADRD-related endophenotype, WGS, infection and covariate information with Year 4 data.** In coordination with the Cores, we will collect all relevant Year 3 data and update the total data

set.

Criteria for Success: Successful transfer and validation of Year 4 cohort data resources and incorporation with prior data.

Rationale: Data needed for updated analyses of Aims 1-3.

Progress: *To be completed.*

Milestone #4-2 **Aim 1. Update empirical relatedness calculation and ancestry estimates.** Using all available data, we will update and store within-population empirical genetic relatedness matrices and within-population ancestry estimates.

Criteria for Success: Successful update of relatedness and ancestry estimates incorporating data from Years 1-4.

Rationale: Derived genetic measures are needed for analyses of Aim 1-3.

Progress: *To be completed.*

Milestone #4-3 **Aim 1. Update disease environment kernel matrix.** Using all available data, we will calculate and store within-population disease environment kernel matrices

Criteria for Success: Successful calculation of relatedness and ancestry estimates incorporating data from Years 1-4.

Rationale: Derived genetic measures are needed for analyses of Aim 1.

Progress: *To be completed.*

Milestone #4-4 **Aim 1. Quantitative genetic analysis of baseline cross-sectional data and longitudinal data from Years 1-4.** Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of heritability for each baseline ADRD-related endophenotype and genetic correlations between endophenotypes. We will also perform cross-sectional and longitudinal (using endophenotypic responses between baseline and 18-month examinations) tests of genotype-by-infection interactions (GEI).

Criteria for Success: Successful preliminary estimation of heritability of baseline ADRD-endophenotypes, genetic correlations between endophenotypes, and both cross-sectional and longitudinal tests of GEI.

Rationale: Establish heritability of focal ADRD-related endophenotypes at baseline and cross-sectional and longitudinal evidence of GEI.

Progress: *To be completed.*

Milestone #4-5 **Aim 1. Update polygenic value estimation and perform GEI tests using WPGVs.** Using all available Year 1-4 data, we will update estimates of WPGVs for each subject for each ADRD-related endophenotype using the mixed model BLUP approach. We will use these in tests of GEI.

Criteria for Success: Successful updating of Year 1-4 WPGVs and WPGV-based tests of GEI.

Rationale: Derived WGPVs are needed for analyses of Aim 1-3.

Progress: *To be completed.*

Milestone #4-6 **Aim 1. Update spatial distance kernels.** We will the spatial distance kernels between all available within-population subjects.

Criteria for Success: Successful implementation of spatial distance calculation and calculation for all Year 1-4. data.

Rationale: Spatial distance matrices are needed for analyses of Aim 1.

Progress: *To be completed.*

Milestone #4-7 **Aim 1. Spatial analysis of baseline cross-sectional data and**

	longitudinal data from Years 1-4. Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of the importance of environmentally determined spatial variation for each baseline ADRD-related endophenotype and longitudinal endophenotypic response measures (using baseline and 18-month examinations).
Criteria for Success:	Successful preliminary estimation of spatial components of baseline ADRD-endophenotypes and 18-month endophenotypic response measures using all Year 1-4 data.
Rationale:	Establish environmental spatial influences on ADRD-related endophenotypes.
Progress:	*To be completed.*

Milestone #4-8	**Aim 2. Update identification and weighting of protein altering and regulatory variation.** As new data accumulate, we will identify new sequence variants that were not previously detected, functionally annotate and incorporate them into gene and gene pathway set.
Criteria for Success:	Successful updating of WGS data and aggregation into genes and gene pathways using data from Years 1-4.
Rationale:	Derived gene and pathway sets are needed for analyses of Aim 2.
Progress:	*To be completed.*

Milestone #4-9	**Aim 2. Update gene and gene pathway kernel matrix estimates and perform gene/gene pathway tests on ADRD-endophenotypes and GEI.** Using all available Year 1-4 data, we will estimate and store gene and pathway kernel matrix estimates using both protein altering variants and putative regulatory variants. We will also use these to test for gene and/or gene pathway specific influences on endophenotypes and their response.
Criteria for Success:	Successful calculation of gene and pathway kernel matrix estimates and initial tests of gene-specific and pathway-specific effects on endophenotypes and GEI measures incorporating data from Years 1-4.
Rationale:	Identification of specific genes and/or gene pathways playing a role in GEI are the focus of Aim 2.
Progress:	*To be completed.*

Project 2 Year 4 Deliverables:

- **Update all existing relevant data for Project 2.**
- **Update empirical relatedness estimates and ancestry estimates using data from Years 1-4.**
- **Update disease (COVID-19) environment kernels estimates using data from Years 1-4.**
- **Obtain preliminary estimates of baseline endophenotype within-population heritability and initial tests of cross-sectional and longitudinal GEI using data from Years 1-4.**
- **Update estimates of WPGVs for each baseline ADRD-endophenotypes and use them in tests of GEI for data from Years 1-4.**
- **Generate spatial distance matrices for data from Years 1-4.**
- **Obtain preliminary estimates of baseline endophenotype within-population spatial components of variability in joint models with genetic factors using data from Years 1-4.**
- **Update functional annotation and develop variant sets for genes and gene pathways using combined data from Years 1-4.**
- **Update gene-specific and pathway-specific sequence variation kernels and perform tests using data from Years 1-4.**

Project 2 Year 5 Milestones

Milestone #5-1	**Aim 1. Finalize quantitative genetic analysis of baseline cross-sectional data and longitudinal data from Years 1-5.** Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of heritability for each baseline ADRD-related endophenotype and genetic correlations between endophenotypes. We will also perform cross-sectional and longitudinal (using endophenotypic responses between baseline and 18-month and 36-month examinations) tests of genotype-by-infection interactions (GEI).
Criteria for Success:	Successful completion of heritability of baseline ADRD-endophenotypes, genetic correlations between endophenotypes, and both cross-sectional and longitudinal variance component-based tests of GEI.
Rationale:	Establish heritability of focal ADRD-related endophenotypes sectional and establish evidence of ADRD-relevant GEI.
Progress:	*To be completed.*
Milestone #5-2	**Aim 1. Finalize joint spatial and genetic analysis of baseline cross-sectional data and longitudinal data from Years 1-5.** Using all available data (including relatedness and ancestry estimates), we will calculate within-population estimates of the importance of environmentally determined spatial variation for each baseline ADRD-related endophenotype and longitudinal endophenotypic response measures (using baseline and 18-month and 36-month examinations).
Criteria for Success:	Successful completion of spatial component analyses of baseline ADRD-endophenotypes and 18-month and 36—month endophenotypic response measures using all Year 1-5 data.
Rationale:	Establish environmental spatial influences on ADRD-related endophenotypes.
Progress:	*To be completed.*
Milestone #4-5	**Aim 1. Finalize GEI tests using WPGVs.** Using all available Year 1-5 data, we will update estimates of WPGVs for each subject for each ADRD-related endophenotype using the mixed model BLUP approach. We will use these in tests of GEI.
Criteria for Success:	Successful completion of WPGV-based tests of GEI.
Rationale:	Establish evidence of ADRD-relevant GEI due to differential response to COVID-19 infection.
Progress:	*To be completed.*
Milestone #5-4	**Aim 2. Finalize gene/gene pathway tests on ADRD-endophenotypes and GEI.** Using all available Year 1-5 data, we will perform final gene and gene pathway specific tests using both protein altering variants and putative regulatory variants in combination with TWAS analysis.
Criteria for Success:	Successful completion of tests of gene-specific and pathway-specific effects on endophenotypes and GEI measures incorporating data from Years 1-5.
Rationale:	Identification of specific genes and/or gene pathways playing a role in ADRD-relevant GEI.
Progress:	*To be completed.*
Milestone #5-5	**Aim 3. Test for the importance of between-population genetic**

	variance in mean response to infection. Using all available Year 1-5 data, we will employ a unified mixed model analysis that will test and estimate between-population genetic variance, within-populaton genetic variance, and GEI. Comparative tests for differences in endophenotypic response to infection between populations will be made for each component. Between-population genetic variance will be structure by empirical between-population genetic similarity matrices.
Criteria for Success:	Successful completion of tests of the importance of between-population genetic differences in the mean response to COVID-19 infection incorporating data from Years 1-5.
Rationale:	Identification of genetically based population differences in ADRD-relevant GEI.
Progress:	*To be completed.*

Project 2 Year 5 Deliverables:

- **Conduct endophenotype within-population heritability analyses and conduct tests of cross-sectional and longitudinal GEI using final data.**
- **Conduct novel WPGV-based tests of GEI for each baseline ADRD-endophenotypes using all final data.**
- **Conduct endophenotype within-population spatial component analyses in joint models with genetic factors using final data.**
- **Conduct analyses to identify specific genes and/or gene pathways that play a role in ADRD-relevant GEI.**
- **Conduct mixed model analyses to examine between-population genetic differences influence differential response to COVID-19 infection.**

Project 3 Milestones

MPIs: Peter T. Fox MD **Co-Is Sidath Kumarapperuma Ph.D**
Felipe S Salinas PhD **John Moring PhD**
Mohamad Habes PhD

SPECIFIC AIMS: Project 3 (Neural Signatures of COVID-19)

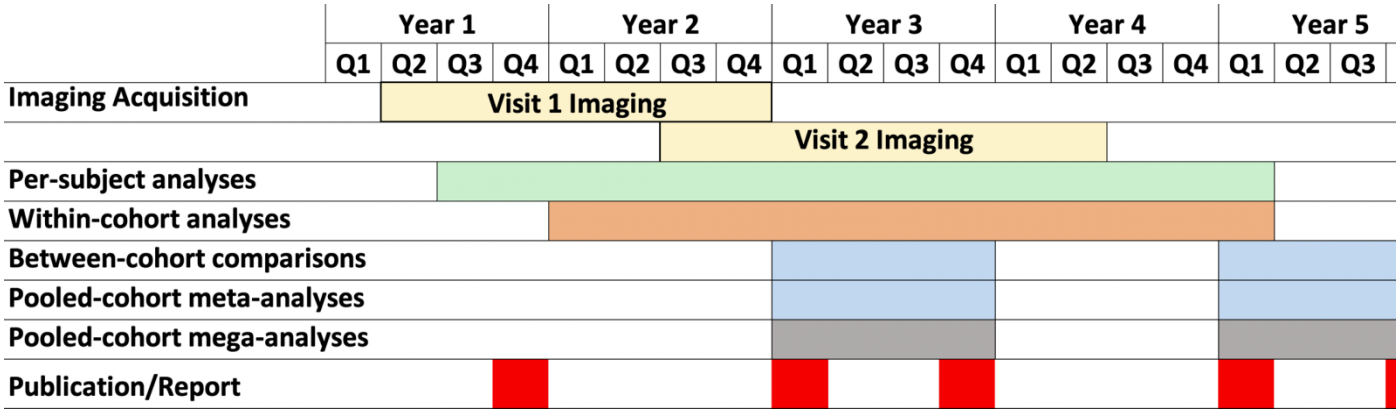
We will employ group-wise analytic strategies measuring: 1) gray-matter functional alterations using functional MRI (fMRI) and PET; 2) gray-matter atrophy using structural MRI (sMRI); and, 3) white-matter abnormalities using sMRI.

Aim 1: Gray-matter Functional Signature & Connectomics. Gray-matter functional alterations will be evaluated using voxel-based physiological (VBP) metrics computed from BOLD fMRI times series. BOLD-based VBP metrics will be supplemented by fMRI blood flow (BF) in all cohorts and PET measures of glucose metabolic rate (MRglu) in the 3 US cohorts, for cross validation. Connectomic alterations will be assessed by group independent components analysis (GICA) and structural equation modeling (SEM) of T2* BOLD time series.

Aim 2: Gray-matter Structural Signature. Gray-matter structural alterations (atrophy and hypertrophy) will be evaluated using both volumetric and surface-based analyses.

Aim 3: White-matter Structural Signature. White matter integrity will be evaluated using tract-based, volumetric, and lesion-counting analytics.

Aim 4 Exploratory analyses. Features discovered through group-wise contrasts (Aims 1-3) will be tested for overlap with known patterns (e. g. EON, AD/MCI, healthy aging, metabolic syndrome, immune mediated, etc.). They will be tested at the per-subject level as predictors of group membership (COVID +/-; cognitive impairment +/-) and shared as quantitative biomarkers and endophenotypes with Projects 1 and 2.



Project 3 Year 1 Milestones

Milestone #1-1 **Aim 1. Establish data access routes.** In coordination with the Cores, we will develop operating procedures for transferring data for analysis.
Criteria for Success: Successful access to Year 1 cohort data resources.
Rationale: Data needed for analyses of Aims 1-3.
Progress: *To be completed.*

Milestone #1-2 **Aim 1. Perform quality analysis of ~400 Amerindians, 50 African, and 100 admixed Hispanic and African American visit 1 brain MRI data.**
Criteria for Success: Successful acquisition and transfer of harmonized brain MRI data from

all sites renders comparable sets from all cohorts.
Rationale: Provide initial characterization of brain MRI data from the ISAVRAD cohort.
Progress: *To be completed.*

Milestone #1-3 **Aim 1. Initiate year 1 per subject neural signature analysis.**
Criteria for Success: Cross-validation of BOLD-based Voxel Based Physiological metrics against Blood Flow (ASL fMRI; all cohorts) and measures of glucose metabolic rate (MRglu 18FDG PET). Within-subject, between-region comparisons will be performed at the per-subject level and per-site group levels. Inter-subject covariance maps of BOLD-based metrics, MRglu, and CBF analyses will be performed at the group-level. Interaction between BOLD and VBP metrics will be evaluated with mutual information analyses in the same manner as the pilot data. Test-retest reliability of BOLD-VBP association within-subjects will be tested by data-splitting in the BOLD and ASL time series.
Rationale: Data needed for analyses of Aim 1, and for Projects 1 and 2.
Progress: *To be completed.*

Milestone #1-4 **Aim 2. Establish pipeline for grey matter structural signatures.**
Criteria for Success: For volumetric analyses group-wise, structural gray-matter differences will be assessed in a voxel-wise manner. Significant group statistical maps will be correlated with difference scores, regional volumes, symptom severity, and genetic deviation. For surface-based analyses, per-subject, cortical thickness maps will be used for intersubject/ group averaging and inference of the cortical surface.
Rationale: Derived morphometric measures are needed for analyses of Aim 2 and for Projects 1 and 2.
Progress: *To be completed.*

Milestone #1-5 **Aim 3. Establish pipeline for white matter structural signatures.**
Criteria for Success: Tract-based Spatial Statistics (TBSS) will be performed using the per-subject Fractional Anisotropy, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps provided by Core 2 (NIC). White-matter volume estimates will use preprocessed data from Core 2 to identify structural white-matter differences in a voxel-wise manner. White-matter Hyper-intensity Distributions volumes provided by Core 2 (NIC) will be used to quantify the increment in brain age acceleration.
Rationale: Derived morphometric measures are needed for analyses of Aim 3 and for Projects 1 and 2.
Progress: *To be completed.*

Milestone #1-6 **Aim 4. Establish pipeline for exploratory analysis.**
Criteria for Success: Map-wise comparisons will be compared to known patterns/disease signatures including AD/MCI, healthy aging, metabolic syndrome, and immune-mediated disease.
Rationale: Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.
Progress: *To be completed.*

Project 3 Year 1 Deliverables:

- **Create and test data access and transfer routes from generating Cores 2, 3 and 4.**
- **Perform QA of initial images (~15%) from all clinical sites.**
- **Implement pipeline for per subject signatures, white matter, grey matter and tractography analysis on existing Year 1 data**

- **Implement a pipeline for exploratory analysis.**

Project 3 Year 2 Milestones

Milestone #2-1	**Aim 1. Update data access routes.** In coordination with the Cores, we will update transferring of curated data for analysis regularly.
Criteria for Success:	Successful access to Year 1-2 cohort data resources (4,300 MRI data sets)
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #2-2	**Aim 1. Perform quality analysis of 3,000 Amerindians, 300 African, and 1,000 admixed Hispanic and African American visit 1 brain MRI data.**
Criteria for Success:	Successful acquisition and transfer of harmonized brain MRI data from all sites renders comparable sets from all cohorts.
Rationale:	Provide initial characterization of brain MRI data from the ISAVRAD cohort.
Progress:	*To be completed.*
Milestone #2-3	**Aim 1. Continue per subject neural and initiate within cohort signature analysis (visit 1).**
Criteria for Success:	Cross-validation of BOLD-based Voxel Based Physiological metrics against Blood Flow (ASL fMRI; all cohorts) and measures of glucose metabolic rate (MRglu 18FDG PET). Within-subject, between-region comparisons will be performed at the per-subject level and per-site group levels. Inter-subject covariance maps of BOLD-based metrics, MRglu, and CBF analyses will be performed at the group-level. Interaction between BOLD and VBP metrics will be evaluated with mutual information analyses in the same manner as the pilot data. Test-retest reliability of BOLD-VBP association within-subjects will be tested by data-splitting in the BOLD and ASL time series.
Rationale:	Data needed for analyses of Aim 1, and for Projects 1 and 2.
Progress:	*To be completed.*
Milestone #2-4	**Aim 2. Initiate preliminary analysis of grey matter structural signatures at baseline (visit 1).**
Criteria for Success:	For volumetric analyses group-wise, structural gray-matter differences will be assessed in a voxel-wise manner. Significant group statistical maps will be correlated with difference scores, regional volumes, symptom severity, and genetic deviation. For surface-based analyses, per-subject, cortical thickness maps will be used for intersubject/ group averaging and inference of the cortical surface.
Rationale:	Derived morphometric measures are needed for analyses of Aim 2 and for Projects 1 and 2.
Progress:	*To be completed.*
Milestone #2-5	**Aim 3. Initiate preliminary analysis of white matter structural signatures at baseline (visit 1).**
Criteria for Success:	Tract-based Spatial Statistics (TBSS) will be performed using the per-subject Fractional Anisotropy, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps provided by Core 2 (NIC). White-matter volume estimates will use preprocessed data from Core 2 to identify structural white-matter differences in a voxel-wise manner.

White-matter Hyper-intensity Distributions volumes provided by Core 2 (NIC) will be used to quantify the increment in brain age acceleration.

Rationale: Derived morphometric measures are needed for analyses of Aim 3 and for Projects 1 and 2.

Progress: *To be completed.*

Milestone #2-6 **Aim 4. Initiate preliminary exploratory analysis at baseline (visit 1).**

Criteria for Success: Map-wise comparisons will be compared to known patterns/disease signatures including AD/MCI, healthy aging, metabolic syndrome, and immune-mediated disease.

Rationale: Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.

Progress: *To be completed.*

Project 3 Year 2 Deliverables:

- **Create and test data access and transfer routes from generating Cores 2, 3 and 4.**
- **Perform QA of all visit 1 images (n= 4,300) from all clinical sites.**
- **Initiate per subject signatures, white matter, grey matter and tractography analysis on visit 1 data**
- **Initiate visit 1 exploratory analysis.**

Project 3 Year 3 Milestones

Milestone #3-1 **Aim 1. Update data access routes.** In coordination with the Cores, we will update transferring of curated data for analysis regularly.

Criteria for Success: Successful access to Year 1-2 cohort data resources (4,300 MRI data sets)

Rationale: Data needed for analyses of Aims 1-3.

Progress: *To be completed.*

Milestone #3-2 **Aim 1. Perform quality analysis of ~15% of visit 2 brain MRI data.**

Criteria for Success: Successful acquisition and transfer of harmonized brain MRI data from all sites renders comparable sets from all cohorts.

Rationale: Provide initial characterization of brain MRI data from the ISAVRAD cohort.

Progress: *To be completed.*

Milestone #3-3 **Aim 1. Continue per subject and within cohort, and initiate between cohort, neural signature analysis in the complete dataset of visit 1.**

Criteria for Success: Cross-validation of BOLD-based Voxel Based Physiological metrics against Blood Flow (ASL fMRI; all cohorts) and measures of glucose metabolic rate (MRglu 18FDG PET). Within-subject, between-region comparisons will be performed at the per-subject level and per-site group levels. Inter-subject covariance maps of BOLD-based metrics, MRglu, and CBF analyses will be performed at the group-level. Interaction between BOLD and VBP metrics will be evaluated with mutual information analyses in the same manner as the pilot data. Test-retest reliability of BOLD-VBP association within-subjects will be tested by data-splitting in the BOLD and ASL time series.

Rationale: Data needed for analyses of Aim 1, and for Projects 1 and 2.

Progress: *To be completed.*

Milestone #3-4 **Aim 2. Continue preliminary analysis of grey matter structural signatures at baseline (visit 1).**

Criteria for Success:	For volumetric analyses group-wise, structural gray-matter differences will be assessed in a voxel-wise manner. Significant group statistical maps will be correlated with difference scores, regional volumes, symptom severity, and genetic deviation. For surface-based analyses, per-subject, cortical thickness maps will be used for intersubject/ group averaging and inference of the cortical surface.
Rationale:	Derived morphometric measures are needed for analyses of Aim 2 and for Projects 1 and 2.
Progress:	*To be completed.*

Milestone #3-5	**Aim 3. Continue preliminary analysis of white matter structural signatures at baseline (visit 1).**
Criteria for Success:	Tract-based Spatial Statistics (TBSS) will be performed using the per-subject Fractional Anisotropy, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps provided by Core 2 (NIC). White-matter volume estimates will use preprocessed data from Core 2 to identify structural white-matter differences in a voxel-wise manner. White-matter Hyper-intensity Distributions volumes provided by Core 2 (NIC) will be used to quantify the increment in brain age acceleration.
Rationale:	Derived morphometric measures are needed for analyses of Aim 3 and for Projects 1 and 2.
Progress:	*To be completed.*

Milestone #3-6	**Aim 4. Continue preliminary exploratory analysis at baseline including pooled-cohort meta analyses and mega-analyses (visit 1).**
Criteria for Success:	Map-wise comparisons will be compared to known patterns/disease signatures including AD/MCI, healthy aging, metabolic syndrome, and immune-mediated disease.
Rationale:	Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.
Progress:	*To be completed.*

Project 3 Year 3 Deliverables:

- **Update and maintain data access and transfer routes from generating Cores 2, 3 and 4.**
- **Perform QA of ~15 % visit 2 images from all clinical sites.**
- **Continue per subject signatures, white matter, grey matter and tractography analysis on visit 1 data**
- **Continue visit 1 exploratory analysis: Pooled cohort meta analysis and mega analysis on visit 1 data.**

Project 3 Year 4 Milestones

Milestone #4-1	**Aim 1. Update data access routes.** In coordination with the Cores, we will update transferring of curated data for analysis regularly.
Criteria for Success:	Successful access to Year 1-3 cohort data resources (4,300 MRI data sets from visit 1 and ~3,000 from visit 2)
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*

Milestone #4-2	**Aim 1. Perform quality analysis of 100% of visit 2 brain MRI data.**
Criteria for Success:	Successful acquisition and transfer of harmonized brain MRI data from all sites renders comparable sets from all cohorts.
Rationale:	Provide initial characterization of brain MRI data from the ISAVRAD

cohort.

Progress: *To be completed.*

Milestone #4-3 **Aim 1. Continue per subject, within cohort and between cohort neural signature analysis in the complete dataset of visit 1 and visit 2.**

Criteria for Success: Cross-validation of BOLD-based Voxel Based Physiological metrics against Blood Flow (ASL fMRI; all cohorts) and measures of glucose metabolic rate (MRglu 18FDG PET). Within-subject, between-region comparisons will be performed at the per-subject level and per-site group levels. Inter-subject covariance maps of BOLD-based metrics, MRglu, and CBF analyses will be performed at the group-level. Interaction between BOLD and VBP metrics will be evaluated with mutual information analyses in the same manner as the pilot data. Test-retest reliability of BOLD-VBP association within-subjects will be tested by data-splitting in the BOLD and ASL time series.

Rationale: Data needed for analyses of Aim 1, and for Projects 1 and 2.

Progress: *To be completed.*

Milestone #4-4 **Aim 2. Continue analysis of grey matter structural signatures (visits 1 and 2).**

Criteria for Success: For volumetric analyses group-wise, structural gray-matter differences will be assessed in a voxel-wise manner. Significant group statistical maps will be correlated with difference scores, regional volumes, symptom severity, and genetic deviation. For surface-based analyses, per-subject, cortical thickness maps will be used for intersubject/ group averaging and inference of the cortical surface.

Rationale: Derived morphometric measures are needed for analyses of Aim 2 and for Projects 1 and 2.

Progress: *To be completed.*

Milestone #4-5 **Aim 3. Initiate analysis of white matter structural signatures at baseline (visits 1 and 2).**

Criteria for Success: Tract-based Spatial Statistics (TBSS) will be performed using the per-subject Fractional Anisotropy, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps provided by Core 2 (NIC). White-matter volume estimates will use preprocessed data from Core 2 to identify structural white-matter differences in a voxel-wise manner. White-matter Hyper-intensity Distributions volumes provided by Core 2 (NIC) will be used to quantify the increment in brain age acceleration.

Rationale: Derived morphometric measures are needed for analyses of Aim 3 and for Projects 1 and 2.

Progress: *To be completed.*

Milestone #4-6 **Aim 4. Continue exploratory analysis at baseline (visits 1 and 2).**

Criteria for Success: Map-wise comparisons will be compared to known patterns/disease signatures including AD/MCI, healthy aging, metabolic syndrome, and immune-mediated disease.

Rationale: Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.

Progress: *To be completed.*

Project 3 Year 4 Deliverables:

- **Update and maintain data access and transfer routes from generating Cores 2, 3 and 4.**

- **Perform QA of ~15 % visit 2 images from all clinical sites.**
- **Continue per subject signatures, white matter, grey matter and tractography analysis on visit 1 data**
- **Complete visit 1 exploratory analysis: Pooled cohort meta analysis and mega analysis.**

Project 3 Year 5 Milestones

Milestone #5-1	**Aim 1. Update data access routes.** In coordination with the Cores, we will update transferring of curated data for analysis regularly.
Criteria for Success:	Successful access to Year 1-3 cohort data resources (4,300 MRI data sets from visit 1 and ~3,000 from visit 2)
Rationale:	Data needed for analyses of Aims 1-3.
Progress:	*To be completed.*
Milestone #5-2	**Aim 1. Complete per subject, within cohort and between cohort neural signature analysis in the complete dataset of visit 1 and visit 2.**
Criteria for Success:	Cross-validation of BOLD-based Voxel Based Physiological metrics against Blood Flow (ASL fMRI; all cohorts) and measures of glucose metabolic rate (MRglu 18FDG PET). Within-subject, between-region comparisons will be performed at the per-subject level and per-site group levels. Inter-subject covariance maps of BOLD-based metrics, MRglu, and CBF analyses will be performed at the group-level. Interaction between BOLD and VBP metrics will be evaluated with mutual information analyses in the same manner as the pilot data. Test-retest reliability of BOLD-VBP association within-subjects will be tested by data-splitting in the BOLD and ASL time series.
Rationale:	Data needed for analyses of Aim 1, and for Projects 1 and 2.
Progress:	*To be completed.*
Milestone #4-4	**Aim 2. Complete analysis of grey matter structural signatures (visits 1 and 2).**
Criteria for Success:	For volumetric analyses group-wise, structural gray-matter differences will be assessed in a voxel-wise manner. Significant group statistical maps will be correlated with difference scores, regional volumes, symptom severity, and genetic deviation. For surface-based analyses, per-subject, cortical thickness maps will be used for intersubject/ group averaging and inference of the cortical surface.
Rationale:	Derived morphometric measures are needed for analyses of Aim 2 and for Projects 1 and 2.
Progress:	*To be completed.*
Milestone #5-5	**Aim 3. Complete analysis white matter structural signatures at baseline (visits 1 and 2).**
Criteria for Success:	Tract-based Spatial Statistics (TBSS) will be performed using the per-subject Fractional Anisotropy, mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) maps provided by Core 2 (NIC). White-matter volume estimates will use preprocessed data from Core 2 to identify structural white-matter differences in a voxel-wise manner. White-matter Hyper-intensity Distributions volumes provided by Core 2 (NIC) will be used to quantify the increment in brain age acceleration.
Rationale:	Derived morphometric measures are needed for analyses of Aim 3 and for Projects 1 and 2.

Progress: *To be completed.*

Milestone #4-6 **Aim 4. Complete exploratory analysis of visits 1 and 2.**
Criteria for Success: Map-wise comparisons will be compared to known patterns/disease signatures including AD/MCI, healthy aging, metabolic syndrome, and immune-mediated disease.
Rationale: Derived gene and pathway between-person sequence-derived similarity matrices are needed for analyses of Aim 2.
Progress: *To be completed.*

Project 3 Year 5 Deliverables:

- **Update and maintain data access and transfer routes from generating Cores 2, 3 and 4.**
- **Complete per subject signatures, white matter, grey matter and tractography analysis on visits 1 and 2 data**
- **Complete exploratory analysis: Pooled cohort meta analysis and mega analysis of visits 1 and 2.**

SPREADSHEET SUMMARY
AWARD NUMBER: 5U19AG076581-02

INSTITUTION: UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT SAN ANTONIO

Budget	Year 2	Year 3	Year 4	Year 5
Salaries and Wages	$1,175,747	$1,175,747	$1,175,747	$1,175,747
Fringe Benefits	$353,470	$353,470	$353,470	$353,470
Personnel Costs (Subtotal)	$1,529,217	$1,529,217	$1,529,217	$1,529,217
Consultant Services	$4,000	$14,000	$14,000	$14,000
Materials & Supplies	$20,000	$20,000	$20,000	$20,000
Travel	$42,000	$41,000	$41,000	$41,000
Other	$305,280	$301,780	$298,280	$72,780
Subawards/Consortium/Contractual Costs	$5,645,292	$2,913,788	$2,828,164	$2,181,737
Publication Costs	$11,000	$14,000	$14,000	$14,000
ADP/Computer Services	$7,118	$7,118	$7,118	$7,118
TOTAL FEDERAL DC	$7,563,907	$4,840,903	$4,751,779	$3,879,852
TOTAL FEDERAL F&A	$1,046,915	$1,047,538	$1,045,613	$921,588
TOTAL COST	$8,610,822	$5,888,441	$5,797,392	$4,801,440

Facilities and Administrative Costs	Year 2	Year 3	Year 4	Year 5
F&A Cost Rate 1	55%	55%	55%	55%
F&A Cost Base 1	$1,903,482	$1,904,615	$1,901,115	$1,675,615
F&A Costs 1	$1,046,915	$1,047,538	$1,045,613	$921,588

Attachment 7

Human Subjects Data Transfer and Use Terms

Human Subjects Data ("Data") will be exchanged under this Subaward (check all that apply):

☒ From Subrecipient to PTE
☒ From PTE to Subrecipient

1. The Party providing the Data will be referred to as the "Provider," and the Party receiving the Data will be referred to as the "Recipient" as reflected above in this section.
2. The Data to be shared will be Personally Identifiable Information (PII)
3. Provider authorizes Recipient to share the Data as may be required under the data sharing plan for this project, and may be required by the Data Sharing & Access section of this Subaward.
4. Upon completion of the Budget Period End Date Recipient shall retain or destroy the Data as instructed by the Provider; provided, however, that Recipient may retain one (1) archival copy of the Data.
5. Description of Data (Required)

Description of Data:

Patient Demographics:
Name (Last, First)
Date of Birth
Sex
Address
Phone Number
COVID-19 positive test Date of Collection
Underlying Illnesses
Subsequent Laboratory Test Results
Vaccination Status (if available)

PII (that isn't PHI) Additional Terms and Conditions:

Data transferred under this Subaward contains identifiable data elements derived from human subjects and constitutes Personally Identifiable Information ("PII Data"), as that is defined in OMB Memorandum M-17-16 and the Common Rule implementing regulation 45 CFR 46, and is not covered under HIPAA, FERPA, or similar laws or regulations governing personal information that require the addition of special terms beyond those included herein.

Provider certifies that it will only provide PII Data to Recipient after the transfer has been authorized by Provider's IRB.

Notwithstanding any statment herein to the contrary, Provider represents that it has full authority to share the Data with the Recipient and has confirmed that the Statement of Work is consistent with such consents as Provider may have obtained form individuals how are the subjects of the Data.

Recipient may only access, use and disclose data as permitted by this Subaward, the Informed Consent ("ICF"), the IRB-approved protocol ("Protocol"), the Common Rule or as permitted by law.

Recipient must use appropriate technical, administrative, and physical safeguards to prevent use or disclosure of PII Data other than as allowed by this Subaward.

Recipient shall only use the Data for the purposes of this Subaward and shall protect the Data from any other unauthorized use and disclosure.

If Recipient becomes aware of any use or disclosure of PII Data not allowed by this Subaward, including if disclosure of PII Data is required by law or court order, Recipient will notify Provider as soon as possible, and in no event later than five (5) business days after its discovery. Recipient will reasonably cooperate with Provider in taking all appropriate or required steps to minimize the impact of any disclosure of PII Data. Provider may have an obligation to make further notifications under applicable state law and Recipient shall cooperate with the Provider to the extent necessary to enable Provider to meet all such obligations.

Recipient will not use PII Data to contact any individuals who are or may be the sources of PII Data without specific written approval from Provider and appropriate IRB approval.

Recipient will remove and securely destroy or return, as directed by the Provider, the part or parts of the PII Data that identifies the individual who is the subject of the PII Data at the earliest time at which removal and destruction or return can be accomplished, consistent with the purpose of the Project.

Recipient will remain in compliance with all applicable U.S. federal, state, and local laws and regulations regarding handling or storing PII Data and record retention requirements.

Sample Invoice

SUBRECIPIENT:

PAYMENT ADDRESS:

_____

_____

_____

_____

DATE:

INVOICE NO.

AGREEMENT NO.

AWARD AMOUNT:

Submit invoice to:
Subaward-invoices@uthscsa.edu

BILLING PERIOD:

_____ to _____

Billing for the period	**Awarded Budget**	**CURRENT**	**CUMULATIVE**
Personnel			
Consultant Costs			
Equipment			
Materials & Supplies			
Travel			
Other Direct Costs			
Subtotal			
F&A Costs			
TOTAL			

I certify that this request represents actual costs incurred during the invoice period and that these costs are appropriate and in accordance with this Agreement. The Subrecipient further certifies that payment made by Prime Recipient under this Agreement shall not duplicate reimbursement of costs and services that are received from other sources.

Signed:_____

Subrecipient authorized financial official

UT Health San Antonio

Supplier # _____
Prenote date _____
Approved_____

PAYEE DIRECT DEPOSIT AUTHORIZATION FORM

A. PAYEE INFORMATION

Federal Employer Identification Number (FEIN) Or Social Security Number (SSN): 74-6001573	
Payee Name: City of Laredo	
Mailing Address: 1110 Houston St.	
City/State: Laredo, TX	Zip Code: 78040
Email Address (to be used for remit advice): jjoly@ci.laredo.tx.us	Phone Number: 956-791-7328

B. FINANCIAL INSTITUTION INFORMATION

Name of your Financial Institution: PNC Bank
Type of account to wish your funds to be directly deposited (check one):

■ **CHECKING.**
Account #: 4947409907 Transit Routing #: 071921891

☐ **SAVINGS.** Account #:_____ Transit Routing #:_____

C. TRANSACTION INFORMATION

☑ **AUTHORIZATION.** Pursuant to section 403.016, Texas Government Code, I authorize UT Health San Antonio to deposit payments owed to me by the University to my financial institution electronically. I understand that the University will, if necessary, reverse and/or make adjustments for any payments deposited in error. I further understand that the University will comply, at all times, with the National Clearing House Association Rules and Regulations governing ACH payments.

☐ **CANCELLATION.** I hereby cancel the authorization for payment by electronic transfer.

☐ **CHANGE.** I hereby request a change of the authorization for payment by electronic transfer.

- Change in account number (same bank) from # to #
- Change in financial institution.
- Change account type (from savings to checking or checking to savings).

I understand that UT Health San Antonio will send me an e-mail notification one business day prior to the payment posting to my account. I understand that notifications may include payment information that is considered confidential and therefore exempt from public disclosure.

Authorized Signature_____ **Date** 10/18/2024

Contact Name/Title Assistant Director of Financial Services