Milestone Report

Deliverables

- **D3.1 A-CC-wide Regulatory approvals plan**

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Version History

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IC = Infrastructure Core, DRC = Data and Research Core, DSTC = Data Science Training Core, L/AC = Leadership Core

AIM-AHEAD IRB Protocol Overview

Background:

The National Institutes of Health's Artificial Intelligence/Machine Learning Consortium to Advance Health Equity and

Researcher Diversity (AIM-AHEAD) program has established mutually beneficial, coordinated, and trusted partnerships to enhance the participation and representation of researchers and communities currently underrepresented in the development of AI/ML models and to improve the capabilities of this emerging technology, beginning with electronic health records (EHR) and extending to other diverse data to address health disparities and inequities. The core components of AIM-AHEAD including partnerships, research, infrastructure and data science training represent a large number of entities participating and engaging in a diverse set of activities that may involve human subjects research that require IRB protocol review and oversight.

The NIH has mandated that all domestic multi-site research funded by the NIH will be required to have a single IRB of record. Per the NIH, "the use of a single IRB of record for multi-site studies that are conducting the same protocol will help streamline the IRB review process by eliminating the unnecessary repetition of those reviews across sites." Aside from the NIH mandate, the revised Federal Policy for the Protection of Human Subjects Common Rule states that most federally funded collaborative research projects located in the U.S. now require use of a single IRB (commercial, academic, or hospital-based) as of January 20, 2020.

Single IRB

Following the mandates of the NIH and the revised Federal Policy for the Protection of Human Subjects (Common Rule), we will adopt the use of a single IRB for all AIM-AHEAD protocols when more than one entity is participating in human subjects research. The AIM-AHEAD project expects the need for many protocols to cover the various planned activities. The IRB of record can be any site participating in a specific activity. It is not assumed that one institution will be the IRB of record for all protocols. AIM-AHEAD Leadership core will identify institutions who have prior experience of serving as Single IRB of record as needed to serve as IRB of record when involved in projects.

The goal for AIM-AHEAD is to use one single IRB (IRB of record) for all protocols. This will provide a set of processes for IRB protocol submission, Standard Operating Procedures/templates, workflows and timelines for submitting IRBs for use in the AIM-AHEAD program. While this is a goal, it is not a set requirement and an assessment and evaluation will be conducted by the IRB working group to determine if having a single IRB that reviews all protocols for the program is feasible and accessible to the majority of members.

Smart IRB

SMART IRB (https://smartirb.org/) is a platform designed to ease common challenges associated with initiating multi-site research. SMART IRB provides a **Reliance Agreement model** that is widely used and **freely** available for institutions and investigators. SMART IRB is an integrated, comprehensive platform that allows flexibility in the size and scope of collaboration to enable IRB reliance for multi-site studies across the nation, regardless of funding status. SMART IRB Agreement can be used for a variety of studies requiring a single IRB, and not just those receiving NIH funding. It can also be used when an Independent (commercial) IRB has been selected as the IRB of Record. Given the wide adoption of SMART IRB, the flexibility of platform, and the well developed joinder process, we will use SMART IRB as the reliance mechanism for AIM-AHEAD.

SMART IRB Participating institutions (935 as of 12/15/2021)

Table 1: Participating AIM-AHEAD sites that are part of SMART IRB

Site Name	Site City	Site State
Case Western Reserve University	Cleveland	OH

Duke University Health System	Durham	NC
Georgetown University	Washington	DC
Georgia Institute of Technology	Atlanta	GA
Harvard Medical School (HMS) and Harvard School of Dental Medicine (HSDM)	Boston	MA
Howard University	Washington	DC
Icahn School of Medicine at Mount Sinai	New York City	NY
Johns Hopkins University School of Medicine	Baltimore	MD
MedStar Health Research Institute	Hyattsville	MD
Meharry Medical College	Nashville	TN
Morehouse School of Medicine	Atlanta	GA
OCHIN, Inc	Portland	OR
Stanford University	Palo Alto	CA
Temple University	Philadelphia	PA
University of California, Irvine	Irvine	CA
University of California, Los Angeles (UCLA)	Los Angeles	CA
University of California, San Francisco (UCSF)	San Francisco	CA
University of Colorado Denver I Anschutz Medical Campus	Aurora	CO
University of Maryland Baltimore	Baltimore	MD
University of Maryland, College Park	College Park	MD
University of Miami	Miami	FL
University of North Texas HSC	Fort Worth	TX
University of Texas, Southwestern Medical Center	Dallas	TX
Vanderbilt University Medical Center	Nashville	TN
Will continue to add AIM-AHEAD sites signed on to SMART IRB as new partnerships are formed or institutions join.		

Exceptions to use of Single IRB

While the goal is to use a Single IRB review for all AIM-AHEAD protocols, the unique and diverse institutions

participating in this project may be unable to rely on another institution's IRB. As such there will be exceptions to allow for sites to use their own IRB to review protocols. In cases where one site prefers to perform an internal IRB review, a single review will still be utilized with other participating sites that are able to rely on another site. When these exceptions occur, sites providing their individual review will submit the same protocols and documents for review as the sites participating in the single IRB review. Once an IRB determination is made, the site will submit their IRB approval letter to the IRB of record for other participating sites.

Process for Sites with no IRB

There are sites within the AIM-AHEAD program that do not have an IRB. In these cases, we will refer sites to a private commercial IRB to allow them to participate in human subjects research and remain compliant with required research procedures. Private commercial IRBs that belong to the SMART IRB will be shared with sites. Sites will have the option to choose which IRB they prefer based on specific characteristics, and no one commercial IRB will be singled out for use of this program. Leadership core of AIM-AHEAD will provide adequate support as and when needed by such sites.

Tribal data sharing/sovereignty

This paragraph is also copied in AIM-AHEAD D3.4 Develop a Data Management and Sharing Plan for Research Data
Any modification in the following paragraph should also be made in the copied document

Research in American Indian and Alaska Native (AI/AN) communities is timely and valuable. It is crucial to include these underrepresented communities in research, but it poses several unique challenges. Many AI/AN communities view academic research with skepticism, mistrust, or even hostility, in large part because research has historically been done in or on communities rather than with community participation. In the past, some research was conducted without appropriate approvals. In addition, findings were interpreted by researchers without appropriate knowledge or understanding of the communities. Thus, AI/AN research requires a commitment to community participation in the development and administration of research, constancy on the part of PIs and research teams and time, an element that is often in short supply in research. Investigators must see the tribes as partners in the research process and involve tribal leaders and experts in each step to ensure the unique considerations of these communities are represented.

Furthermore, tribes are sovereign Indian Nations that have special, complex relationships with the Federal government. Many discussions, publications, and treatises have addressed how this relationship affects the ownership and sharing of data. The growing consensus on the part of tribal communities is that the Indian Nations have an inherent right to at least an equal say in the fate of raw data. Investigators must recognize these rights and establish procedures and timeframes to comply with administrative and regulatory policies. From a purely logistical perspective, it typically requires more time to negotiate and complete research than in other communities. For example, an investigator may seek approvals from 1 or 2 institutions when conducting research in non-Native populations. Additional levels of review may be needed in AI/AN settings.

Listed below are the types of reviews that may be conducted for data obtained through AI/AN community organizations and urban Indian health organizations (UIHO), including urban Indian clinics, and through Indian Health Service (IHS) and tribally operated hospitals and clinics, which obtain the vast majority of their funding from IHS.

Research conducted using data from UIHOs and AI/AN community organizations include one's own Institutional Review Board (IRB), the Research Review and Privacy Boards of the UIHOs and community organizations, and in some cases cultural review boards. Local stakeholder support for the research project can be equally critical to securing approvals. Stakeholders may include Community Health Representatives, local opinion leaders, and other widely respected culture-bearers. The effort required to establish sampling frames, craft regulatory and data sharing agreements, obtain permissions, build trust, and recruit AI/AN participants can be prohibitive unless community partnerships and collaborations are already in place.

Many UIHOs and AI/AN community organizations serve AI/AN peoples from different tribal backgrounds and are not affiliated with a single tribal or IHS IRB or Research Review Board (RRB), or a tribal council. If a research project involves data from an IHS or tribally operated health facility or organization, approvals from an IHS IRB (national or local), the tribal IRB or RRB, or tribal council if no tribal IRB or RRB exists, are needed. Historically, IHS and tribes do not cede oversight of research to another institution, making the use of a single IRB with these communities impossible. In addition, UIHOs, tribal organizations, and IHS may require a data use agreement be enacted for the project.

We view these organizations as participating in AIM-AHEAD as full partners with the investigators. Thus, decisions about sharing of data cannot be made without full discussion and agreement by the participating tribes or organizations. We have concluded that each tribe or tribal partner must approve all provisions laid down in such policies prior to the release of data, including individual-level data with or without personal identifiers, to any outside investigator and prior to establishing any secondary databases. With appropriate approvals, non-identifiable data may be aggregated to permit cross-hub/core analyses and dissemination of results which may have immediate relevance to communities.

IRB Protocol Submission Process

Determining if Human Subjects Research Review is needed

Sites participating in the activity will decide if IRB review is needed for the planned activity by way of IRB communication in the form of either IRB memo or formal protocol submission. To assess whether the project is Not Human Subjects Research (NHSR), investigators should **at minimum** submit a memo to their local IRB that details the data source, whether data are fully de-identified, and a general description of the activity; from there, the local IRB will help the investigator identify whether a formal protocol submission is required. An example of this type of communication can be found here. All Pilots and funded Call for Proposals are required to submit a formal determination from their local IRB or a commercial IRB. If you have any questions or concerns about getting an IRB review and determination, please reach out to the Research Compliance Office (RCO). In any instance where human subjects research is occurring, an IRB protocol will be developed and submitted. Only sites participating in the research activity need to be included on the IRB protocol. For AIM-AHEAD IRB protocols it is not expected that all sites will participate in all activities and IRB protocols. All AIM-AHEAD project related protocols will be submitted to AIM-AHEAD leadership core for the purpose of maintaining a central record.

HHS Human Subject Regulations Decision Charts:
https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts-2018/index.html

Research Exemptions from IRB Review

If the research is expected to be exempt, a protocol will be developed and submitted for IRB Review. Much of this research may be exempt from IRB review following initial determination if data and/or samples will have identifiers removed. If, however, identifiable private information or identifiable biospecimens are to be used, broad consent or other requirements may apply.

Full Board Review/Expedited Review

Research that requires a full board or expedited review requires a protocol to be developed and submitted for IRB Review. Additional ancillary approvals relating to data security, use and sharing may additionally be required. Ancillary reviews may benefit by referring to the AIM-AHEAD IT Security Plan, Data Management and Sharing Plan for Research Data and Assessment and inventory of all data resources available to consortium members.

Identifying Participating Sites

Any sites participating in the research activity will be required to be included in the IRB protocol. It is encouraged to promote inclusiveness and transparency in the AIM-AHEAD program and when possible sites should be made aware of the research activity and invited to participate.

Protocol Development

All sites participating in a particular research activity should have the opportunity to review, edit and make additions to the IRB protocol for that planned activity. Each site should identify an Investigator that will serve as contact and represents their site for the planned research activity. The AIM-AHEAD program will work to develop common protocol templates and requirements specific to the AIM-AHEAD initiative.

Choosing IRB of Record

The IRB of record can be any participating site able to provide review for other participating sites. The IRB of record should be participating in an active reliance agreement with the participating institutions. The IRB of record should have appropriate staffing needed to provide review in a timely manner.

Notifying Coordinating Center

The AIM-AHEAD coordinating center should be notified of any new protocols (or protocol modification mentioning AIM-AHEAD) related to the AIM-AHEAD project prior to submission.

List of IRB Protocols for AIM-AHEAD

As activities evolve and develop for AIM-AHEAD IRB protocols will be listed here:
https://docs.google.com/spreadsheets/d/1GJ_WRlvAAH0HnGMWchH9qdG0wv0JK13-acfhKnB6Loc/edit?usp=sharing

Continuing Reviews

The lead site will collect all required updates and documentation for continuing reviews as needed, including providing an updated list of individuals involved in the research activities.

Study Termination

At the end of the study period the IRB protocol will be closed and all appropriate procedures will be followed in accordance with protocol specifications to ensure data retention/storage or destruction in a secure manner.

Related Regulatory Policies and Plans

The AIM-AHEAD program as also created the following regulatory policies and plans that are may be relevant to a specific protocol:

- IT Security Plan,
- Data Management and Sharing Plan for Research Data
- Assessment and inventory of all data resources

OTA Contractual Considerations

A. Human Subjects section from AIM-AHEAD signed OTA

This section is added here for information as a reminder. Cannot be edited without changing OTA contracts.

1) **Data Sharing.**
   The NIH recognizes that data sharing may be complicated or limited, in some cases, by organizational policies, and local, state, and federal laws and regulations, including the HIPAA Privacy Rule (https://www.hhs.gov/hipaa/for-professionals/privacy/index.html). The rights and privacy of individuals who participate in the NIH-sponsored research must be always protected. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. Recipients must exercise great care to ensure that resources involving human cells or tissues do not identify original donors or subjects, directly or through identifiers such as codes linked to the donors or subjects. Also important is compliance with human subjects requirements that apply to the use and sharing of human data (e.g., 45 CFR 46, Article XIII (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html).

2) **Compliance with HIPAA and the Common Rule**
   In the event there are terms in this Agreement which would not comply with HIPAA and/or the Common Rule, the parties agree to amend this Agreement to incorporate mutually acceptable terms and conditions that would resolve the non-compliance.

B. Human Subjects Protection section from AIM-AHEAD signed OTA

This section is added here for information as a reminder. Cannot be edited without changing OTA contracts.

The DHHS regulations for the protection of human subjects, in 45 CFR 46, implement Section 491(a) of the PHS Act and provide a framework, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the NIH or other DHHS components. The DHHS regulations stipulate that the recipient organization(s), whether domestic or foreign, bears ultimate responsibility for safeguarding the rights and welfare of human subjects in DHHS-supported activities (46.101[a] and 46.103[a]). Recipient organization)s) "engaged" in human subject's research must obtain a Federal-Wide Assurance (FWA) with the DHHS Office for Human Research Protections and establish appropriate policies and procedures for the protection of human subjects. The Recipient must obtain Federal Wide Assurance (FWA) from the DHHS Office for Human Research Protections (OHRP) (https://www.hhs.gov/ohrp/register-irbs-and-obtainfwas/fwas/fwa-protection-of-human-subjecct/index.html), and comply with 45 CFR 46 (https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html) and, as applicable, any relevant FDA regulations (e.g., 21 CFR 11, 50, 54, 56, 312, and 812) (https://www.fda.gov/medical-devices/medical-device-databases/code-federal-regulations-title- 21-food-and-drugs)

governing the protection of human subjects and the conduct, management, and oversight of clinical trials. The Recipient shall provide to the OTAO evidence of an active FWA prior to the commencement of any human subject research activities contemplated under this Agreement. Furthermore, the Recipient must comply with all applicable laws and regulations relating to the privacy and confidentiality of human subjects.

C. Institutional Review Board Requirements section from AIM-AHEAD signed OTA

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If applicable, the Recipient agrees to provide a certification to the OTAO that the research application has been approved by an appropriate Institutional Review Board (IRB), consistent with 45 CFR 46 and OHRP guidance. Note that the NIH requires the date of final IRB approval;conditional IRB approval is not sufficient. The PI must ensure that continuing review and reapproval of research occurs prior to the end of the approval period specified by the IRB. Consistent with the NIH Single IRB Policy for Multi-site Research(https://grants.nih.gov/policy/humansubjects/single-irb-policy-multi-site-research.htm), theRecipient also agrees that all sites participating in a multi-site study will rely on an singleInstitutional Review Board (sIRB) to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations at 45 CFR 46. Although IRB ethical review at a participating site would be counter to the intent and goal of this provision, this provision does not prohibit any participating site from duplicating the sIRB. The Recipient furthermore agrees to comply with the OD Guidelines for Consent Forms in Multicenter Clinical Studies (https://www.OD.nih.gov/grants-and-training/policies-and-guidelines/OD-guidelines- forconsent-forms-in-multicenter-clinical-studies).

D. Certificates of Confidentiality section from AIM-AHEAD signed OTA

This section is added here for information as a reminder. Cannot be edited without changing OTA contracts.

Section 301(d) of the PHS Act, as amended by Section 2012 of the 21st Century Cures Act, P.L. 114- 255, states that the Secretary shall issue Certificates of Confidentiality (Certificates) to NIH funded investigators or institutions engaged in biomedical, behavioral, clinical, or other research activities in which identifiable, sensitive information is collected. Recipients that conduct biomedical, behavioral, clinical, or other research that collects or uses identifiable, sensitive information are deemed to be issued a Certificate.

The Recipient is therefore required to protect the privacy of individuals who are subjects of such research in accordance with subsection 301(d) of the Public Health Service Act. Certificates issued in this manner will not be issued as a separate document. For more information, please see the following link: https://grants.nih.gov/policy/humansubjects/coc.htm. The Recipient must obtain and retain personal identifiers on all research participants, to the extent possible, except where prohibited (by Tribal data sovereignty) for future longitudinal follow-up and to be leveraged for intervention research. Data collected from this Program will be protected by a Certificate of Confidentiality. Recipients shall use guidance provided by the ACC for data acquisition, collection, and curation, including appropriate consent for data sharing and implementation of methods to allow data to be AI-ready.