



Protocol Title ***All of Us Research Program***¹

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1 Background and Scientific Rationale

Our current approach to health care is informed by clinical trials that have sample sizes in the thousands, or tens of thousands, meaning that we typically lack the statistical power to make fine-grained predictions about how a given treatment will affect a given individual. As a result, therapies often fail in practice and most interventions fail to integrate with most patients' own knowledge and lifestyles. Historically, this approach is characterized by a lack of inclusion and diversity in clinical study; that is, the benefits of precise and personalized interventions may not be accruing equitably across society.

Precision medicine is an approach to disease prevention, diagnosis, and treatment that seeks to maximize effectiveness by considering individual variability in genes, environment, and lifestyle. Precision medicine seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through the combined analysis of biological, environmental, and behavioral factors that contribute to health and disease. This understanding may lead to more rational disease prevention strategies, more accurate diagnoses, better treatment selection, and the development of novel therapies. The promise of precision medicine can only be achieved with input from a broad population that reflects the true diversity and life experiences of those in the United States.

By combining health-related information from one million or more diverse participants, the *All of Us* Research Program will have the right scale and inclusive scope to enable research for a wide range of diseases, both common and rare. A cohort of this size will have the statistical power to detect associations between genetic and environmental exposures and a wide variety of health outcomes. A deliberately inclusive strategy that prioritizes groups historically underrepresented in biomedical research (UBR) should provide enough power for meaningful subgroup analyses and lead to the most precise medicine for these groups. Outcomes of this research could include novel prevention and screening strategies, earlier and more precise diagnoses, new and more rational use of therapies, and improved understanding of why some people remain healthy despite exposures and risk factors for disease.

Coincident with advancing the science of medicine is a changing culture of health care practice and biomedical research that engages individuals as active partners. The *All of Us* Research Program aims to actively engage participants and their advocates in all aspects of the research program, including governance, oversight, design, conduct, dissemination, and evaluation. Participants will not only provide their biological, health, behavioral, and environmental data, they will also be able to access their information, learn about the research being conducted, and be partners in the discovery process. This ongoing partnership between the research program and participants is described in Section 12, Post-Enrollment Engagement Strategy.

2 Objectives

2.1 What Is the *All of Us* Research Program?

The mission of the *All of Us* Research Program is to advance the science of precision medicine and ensure everyone shares in its benefits. To accomplish this, the *All of Us* Research Program established a set of core values to guide our decisions and actions as the program grows in capacity, reach, and research. We aspire to incorporate these values throughout our journey as our first participants enroll, we collect the first data points, and we plan the first studies:

1. Participation in the *All of Us* Research Program will be open to interested individuals
2. The research program will reflect the rich diversity of America
3. Participants will be partners in the research program
4. Trust will be earned through robust engagement and full transparency
5. Participants will have access to information and data about themselves
6. Data from the research program will be broadly accessible to empower research
7. The research program will adhere to the [PMI Privacy and Trust Principles](#) and the [PMI Data Security Policy Principles and Framework](#)
8. The research program will be a catalyst for innovative research programs and policies

The overall objective of the *All of Us* Research Program is to build a robust research resource that can facilitate the exploration of biological, clinical, social, and environmental determinants of health and disease. The research program will collect and curate health-related data and biospecimens from one million or more individuals who reflect the diversity in the United States; these data and biospecimens will be made broadly available for research uses.

The *All of Us* Research Program is an observational study that will provide the information needed to address a wide range of scientific questions. Resource use is anticipated to be very broad, from the use of aggregate data to the use of individual-level data and biospecimens. This broad usage of data will address a wide range of biomedical and scientific opportunities across diverse populations. Some examples of opportunities that we anticipate can be addressed through judicious use of this resource include:

1. Enabling participants to partake in research by bringing research closer to communities across the country through a direct volunteer approach.
2. Empowering participants with information and data that may improve their own health
3. Making data broadly available to traditional and nontraditional researchers (including nonprofessional or “citizen” scientists) to develop innovative technologies and methodologies
4. Developing quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors, and gene–environment interactions
5. Discovering biomarkers that identify individuals with an increased risk of developing common diseases
6. Optimizing screening and prevention strategies based on individual genomic,

- environmental, and behavioral risk factors
7. Developing tools and approaches for new or improved disease classifications and relationships
 8. Using personal health technologies to correlate sensor data, behavior, and the environment with health outcomes
 9. Identifying the determinants of safety and efficacy for common therapeutics
 10. Using biological data to develop new therapeutic strategies
 11. Inviting participants to enroll in clinical trials of targeted interventions and therapies

3 Study Overview

The *All of Us* Research Program aims to enroll one million or more participants from throughout the United States to provide insight into the substantial interindividual differences in physiology, risk of disease, and response to therapy. Participants will be invited to share their electronic health records, if any, and answer health-related questionnaires. Some participants may also be invited to undergo physical measurements and provide biospecimens from which genomic information and other biomarkers may be derived through analytics. The selection of participants to these modules will be based on the desire for demographic diversity. The information and biospecimens collected will become a useful resource for current and future researchers to investigate why some people develop certain health conditions while others do not.

3.1 Participants Representatives

A central principle of the *All of Us* Research Program vision and promise is to include participants as true partners in all aspects of the program, from research design through governance. Participants will help set the standard for the program to reflect the diverse needs, preferences, and priorities of participants inclusive of the range of age, social, racial, ethnic, cultural, geographical, sexuality, gender, physical abilities, and health statuses of individuals in the United States. AoURP will facilitate meaningful involvement of diverse participant communities in governance and oversight, operations, and communications of the program and enable ongoing input from groups often underrepresented in research. Processes and mechanisms for elevating participant voices will include:

1. **Steering Committee** – Up to five participant representatives and up to five PIs from community partner awards will be members of the steering committee with oversight on the direction and implementation of the program. The 35 voting members of the current steering committee are representatives of program awardees, participant representatives, and NIH.
2. **Advisory Panel** – A working group that provides expert advice on the vision, scientific goals, and operations of the *All of Us* Research Program. Currently, the advisory panel consists of 14 subject matters experts and researchers. The panel meets at a minimum of six times annually (three all-day Face-to-Face meetings, three 1-hour WebEx meetings, and ad hoc meetings as needed). The

- goal is to add at minimum three participant representatives to the advisory panel, for a total of 17 advisory panel members, to represent the perspective of the general public and communities underrepresented in biomedical research. These advisory panel participant representatives will be selected from an “open call” for self-nomination on the Participant Portal.
3. **Executive Committee** – Two participant representatives from the steering committee or the advisory panel will be members of the executive committee also. The EC will be composed of 16 members total.
 4. **AoURP Participant Panel** – We will ask our consortium engagement leads to nominate participant representatives from their respective Participant/Community Advisory Boards to serve on the AoURP Participant Panel. The panel will consist of 24 participants with an emphasis on representing diverse socioeconomic groups, educational backgrounds, needs, and preferences, who will provide feedback and insight about the program to AoURP staff.
 5. **Governance structure** – Representatives serving on our AoURP Participant Panel will have the opportunity to serve on our governing committees, boards, and task forces as appropriate.

To ensure diversity of participant voices, we will create a clear and concise description of participants’ role in each panel and committee and emphasize the importance of diversity to the program. We will include questions in the application or nomination form for individuals to identify communities and perspectives they represent, consider perspectives currently represented in the program, and identify gaps in perspectives not currently represented.

Interested prospective participants on the Advisory Panel and the AoURP Participant Panel will submit a personal statement (self-nominees) or the consortium engagement lead will complete a nomination form, in both cases describing the individual’s background and experience. As a part of the selection process, in addition to filling gaps in perspectives not represented, participant representatives are also expected to be interested in and willing to devote the time needed to learn about the vision, opportunities, and challenges of the *All of Us* Research Program. They must be committed to advancing health and wellness research, particularly for those who have been historically underrepresented in biomedical research (UBR), and they must also have the willingness and ability to work collaboratively with the program’s researchers, physicians, technology experts and staff.

Participant representatives will be invited to serve one 2-year term; however, our goal is to develop a relationship with our participant partners such that they will remain engaged in some capacity throughout the life of our program. This will enable sufficient time for advocates to learn about and help shape the program and also allow opportunities for a diversity of participant advocates to serve and contribute value to the program.

In addition to the Advisory Panel, the AoURP Participant Panel, and involvement in governance, participants can provide feedback and input on the program, including using comment or suggestion boxes at partner sites and contacts and/or email addresses at partner sites. There is an open text box on the Participant Portal for feedback and plans to

send IRB-approved structured surveys to participants to share their experiences. Cognitive Testing and Usability Testing are also used to further enhance participant involvement and experience.

In addition to having participant representatives help shape the *All of Us* Research Program in the ways described above, the program invites participants to become partners in the data gathering and research process through various means, including data return and as “citizen” scientists investigating the data.

The combination of a highly engaged participant population and rich biological, health, behavioral, and environmental data will undoubtedly help the program to develop a key resource for biomedical investigation.

3.2 Creating a Resource for Research

To build the *All of Us* Research Program, we seek to enroll one million or more participants. Interested individuals will be able to enroll in one of two ways; whichever is most convenient for them. See illustration in Figure 3–1: Participant Interaction Flow.

1. Through a participating health care provider organization (HPO). This approach is primarily, but not exclusively, for people who are a member of an HPO’s health plan and their affiliates or have received care at any of several participating health centers across the United States. However, any eligible individual who wishes to enroll at an HPO may do so, even if they do not have a prior connection with that HPO. Participating HPOs were chosen in the peer review process based on their ability to provide a diverse cross-section of the population as well as for their ability to support and quickly enable the technical and scientific requirements of the study.
2. Virtually, as direct volunteers (DVs), for non-HPO members, or for people who are seeking a more convenient place to enroll.

Both the DV and HPOs paths will rely on digital tools developed by the Participant Technology Systems Center (PTSC) and rendered on a smartphone application and/or a research program website to register participants.

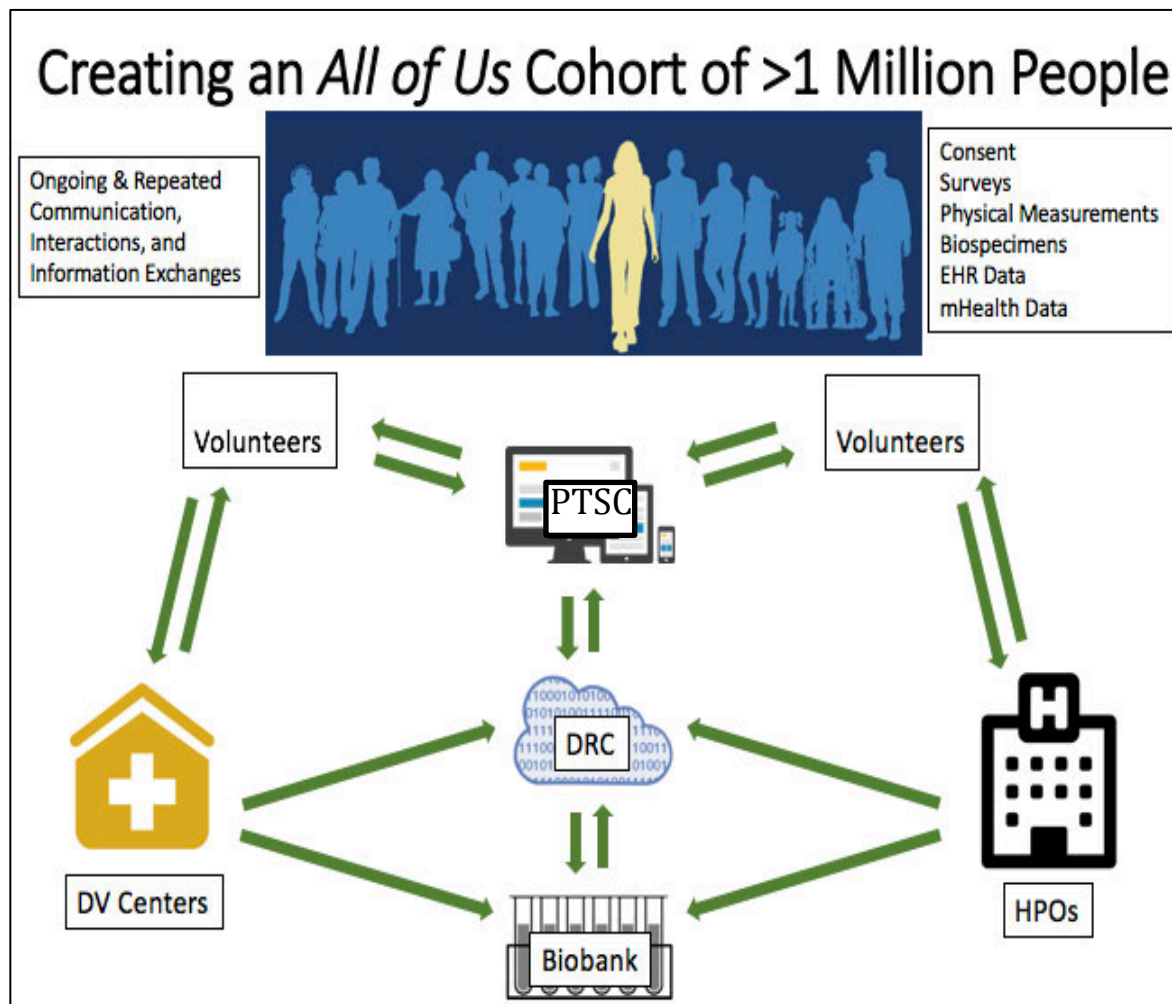
Participants will provide some or all the following:

- Participant-provided information (PPI) via questionnaires and surveys (see Section 7.1, Participant-Provided Information (PPI))
- Electronic health records (EHRs). The *All of Us* Research Program seeks consent to access information from each participant’s EHR. Not all participants will have an EHR, and the process for sharing EHR data to the DRC will differ between members of an HPO or a DV. HPOs will share EHR data with the DRC for their participants following informed consent. Outside of the HPOs, participants will be able to share their EHR data with the DRC via the Sync for Science (S4S) technology that is currently in development (see Section 7.6, Electronic Health Records) or similar technology from other vendors.
- Physical measurements and biospecimens (PM&B). Participants who have agreed to share their EHR data may be invited to provide baseline physical measurements (see Section 7.3, Physical Measurements) and biospecimens

(blood, urine, and/or saliva). Biospecimens will be assayed to generate various biological data, which may be incorporated into participants' study records (see Section 7.4, Biospecimen Collection). In addition, DNA will be isolated from the blood or saliva samples for genetic assays.

- Passive mobile and digital health data (personal health technology data). Additional data may eventually be collected from a subset of participants to be determined, through health, wellness and fitness devices, other sensors, and/or mobile applications (see Section 7.2, Use of Personal Health Technologies).

Figure 3–1: Participant Interaction Flow



3.3 Making the Resource Accessible for Research

The *All of Us* Research Program aims to provide a useful resource that becomes enriched and improved over time. The research program expects to include detailed longitudinal health and exposure information from participants and retains the flexibility to enhance its scope as funding allows.

A core dataset of all data contributed will be developed (see Section 11, Creation of the *All of Us* Research Program Resource). Ideally, in time, the core dataset will include PPI, physical measurements, digital health technology readings (e.g. Fitbit), genomic and

baseline biospecimen assays, and EHR-derived information from most participants. Data elements will be transferred through encrypted channels to the *All of Us* Research Program's Data and Research Center (DRC) for storage and for creating a dataset accessible to researchers. The data will be stored in a secure cloud-computing environment that follows rigorous standards to protect individual privacy and data confidentiality. AoURP will use a variety of approaches to remove explicit personal identifiers such as name, email, phone number, street address, medical record number (MRN) and Social Security number (SSN) from the datasets made available for research purposes, including from free text data sources such as open response fields and EHR notes. The Committee on Access, Privacy, and Security (CAPS) will evaluate these approaches prior to release and routinely control their quality to minimize the risk of inappropriate re-identification. The researcher-accessible dataset will be queried through a dedicated analysis platform, the *All of Us* Research Program Research Portal, for research purposes. The DRC will develop tools to enable analysis of the data within this secure cloud-computing environment. Qualified researchers who wish to access the data will agree to not remove data from the Research Portal without approval. The *All of Us* Research Program will bring researchers to the data rather than asking researchers to download data to their own machines. The Committee on Access, Policy, and Security (CAPS), previously known as the *All of Us* Resource Access Committee (AURAC) will serve as the stewards of the data.

3.4 Study Timeline/Study Duration

The *All of Us* Research Program is expected to last at least 10 years, with active enrollment occurring in the first five years. Follow-up is expected to be continuous for the life of the program. For example, data from EHR will be added to a participant's *All of Us* dataset at least biannually for those who signed the HIPAA Authorization for Research. Participants will not receive notification each time EHR data are added.

Lastly, the data analysis platform (the *All of Us* Research Program Research Portal) will be built and available for use by qualified researchers within the second year and available for the life of the program.

4 Selection of Participants

The full potential of the *All of Us* Research Program will be realized only by reflecting the full diversity of the United States regarding demographics (age, race and ethnicity, education, socioeconomic status), health status (both healthy participants and those with disease), disabilities, and geography.

4.1 Eligibility

All individuals living in the United States or a territory of the United States are eligible to participate, provided they meet the inclusion/exclusion criteria below.

The *All of Us* Research Program recognizes the opportunities and challenges of enrolling a diverse population. Qualifiers of diversity include but are not limited to race, ethnicity, age, sex, gender identity, sexual orientation, disability status, access to care, income, educational attainment, and geographic factors. The research program will actively recruit

minority populations who are historically underrepresented in biomedical research (UBR). The emphasis placed on UBR is an effort to enable rigorous research that may inform policy, prevention, and/or treatment approaches and thereby decrease current health disparities.

While the aim of the *All of Us* Research Program is to engage and enroll participants from all life stages, initial enrollment efforts will center around individuals legally able to consent to participate in research on their own. Any considerations to include a broader population will be addressed in future protocol amendments.

Educational content and consent materials will be available in English and Spanish at the national launch; therefore, initial enrollment efforts will focus on participants who read and speak either English or Spanish. The *All of Us* Research Program explicitly values inclusion; as such, in the future we will release materials translated in other languages reflective of the broader United States population.

Additionally, we will ensure participation is open to persons living with physical disabilities. Site-specific accommodations will be made to ensure that persons living with physical disabilities who meet the inclusion criteria are able to enroll.

4.2 Inclusion and Exclusion Criteria

4.2.1 Inclusion Criteria

- Adults 18 and older with the legal authority and decisional capacity to consent
- Currently residing in the United States or a territory of the United States

4.2.2 Exclusion Criteria

It is the goal of the *All of Us* Research Program to be as inclusive as possible. Although all eligible person should be considered for enrollment, it is crucial that adequate consenting procedures be in place to ensure that the rights, safety, and welfare of all participants enrolled are not compromised.

During this initial enrollment period, and until specific enrollment procedures are developed, the following eligible individuals will be excluded:

- Individuals without the physically capacity to consent
- Prisoners at the time of enrollment

The electronic format of the consent process prevents enrolling individuals without the capacity to use the electronic tools. This situation is temporary but will persist until we adapt the consent process and materials.

We do not intend to enroll prisoners without appropriate oversight by the IRB; however, we recognize that it is possible, even likely, that some participants may become incarcerated over the course of their participation in the *All of Us* Research Program. We believe that prisoners should not bear an unfair share of the burden of participating in research or be excluded from its benefits, to the extent that voluntary participation is possible (Huang et

al., 2017). Participation in the *All of Us* Research Program does not affect participants' rights and is in no way meant to change their social setting or impinge on prison resources or other inmates. Therefore, it is our intention to comply with all relevant federal and state laws, and applicable regulations under subpart C of 45 CFR part 46 for the inclusion of prisoners.

Until further notice from the IRB, the research program material will include a note that people who are incarcerated cannot take part at this time, but that we hope this will change in the future.

4.3 Vulnerable Populations

The vulnerable populations that will be excluded in the initial enrollment efforts are summarized in Table 4–1: Vulnerable Populations Excluded at Launch. Separate protocol amendments will be developed that include plans to enroll vulnerable participants, such as children, prisoners, and cognitively impaired individuals.

Table 4–1: Vulnerable Populations Excluded at Launch

Excluded at Launch	Vulnerable Population
X	Adults unable to consent
X	Children (<18 years old in most US states)
X	Prisoners at time of enrollment

Due to the minimal risk nature of this protocol, if an individual is interested and able to participate in the *All of Us* Research Program, meets the eligibility criteria, and is not specifically excluded, they will not be turned away. For example, adult women living in the United States or a territory of the United States who are capable of consent will not be turned away from participation based on their pregnancy status. If known, pregnancy status will be electronically recorded at the time of the PM&B visit.

5 Recruitment Outreach

To achieve the broad enrollment and participant diversity objectives of the *All of Us* Research Program, we will engage potential participants through a range of outreach approaches. Outreach is defined as all interactions that take place between the research program and potential participants (i.e., in advance of creating a research program account). Potential participants will learn about the *All of Us* Research Program via:

1. Targeted advertisement, including:

- Print brochures
- Web advertisements
- TV advertisements
- Radio advertisements

2. Personal interest groups:

- Social media
- Community events
- Press coverage

3. Directly at HPOs or DV partner sites, including:

- In waiting areas
- During the regular course of clinical care at HPOs
- Local informational events
- Regional informational events organized by research program awardees, HPOs, or DV partners.
- Employee invitations
- Re-contact of consented participants in existing research programs

Potential participants who would like to learn more about the research program will be directed to:

- Trained research program staff at HPO sites
- The *All of Us* Research Program Support Center
- The *All of Us* website (<http://joinallofus.org>)

Web-based materials (assets) will be especially important, given the broad geographic scope and the large numbers of prospective participants needing to be engaged to meet the one million or more enrollment goal. IRB-approved information materials targeted to the general public will be available on the *All of Us* website, including:

- Branding and animation videos about the research program
- Anthem video, with or without English or Spanish subtitles
- Community videos
- Frequently asked questions
- Messages from program leadership (e.g., the master narrative)
- Testimonials from participants

These assets are available on the Wondros *All of Us* Asset Portal (AllOfUsAssetPortal.org) to be used across the research program in accordance with guidance from the IRB:

- IRB-approved assets may be “mixed and matched” to create new assets that are a composite of elements of previously approved assets
- All assets used must clearly indicate, and emphasize, that the activity is research
- When combining assets, the overall tone, messages, and ethos of the original combination of assets cannot be altered

5.1 Outreach to HPO Members

HPOs may use both nationally and locally developed outreach approaches to engage their patient population, members of their health plan or of an affiliate, and any interested eligible individuals in their catchment area. HPOs will be able to use approved research program advertising materials as is or co-brand these materials following guidelines (such as images, look, and feel). They may also use locally developed outreach materials that speaks to their local community. All locally developed outreach materials will be presented to the IRB as part of the Institution-Specific IRB Application (ISIA) process. Potential participants interested in enrolling through an HPO will be provided with contact information for trained research program staff via email or phone, listed on the

advertisement. Interested parties can also follow the link to the research program website or mobile application for more information. As a condition of their NIH award, HPO awardees must affirm:

- They will not add non-HPO members who enroll in AoURP through their sites to the HPO's general operations marketing list
- They will not add non-HPO members who enroll in AoURP through their sites to the HPO's advertising lists
- They will not recruit non-HPO members to join the HPO health system

5.2 Outreach to Direct Volunteers

To complement the regional efforts of the HPOs, The Participant Center (TPC) will develop the strategies to engage direct volunteers. TPC team is led by Scripps Translational Science Institute (STSI) and supported by Walgreens, WebMD, the Blue Cross Blue Shield Association (BCBSA), the National Blood Collaborative, and others. TPC outreach efforts will use approved national and/or customized advertising materials and a multi-pronged strategy for outreach to historically underrepresented populations in biomedical research. The TPC approach will be designed to enroll people across the country and, in particular, focus on underrepresented populations (UBR) and those in areas not serviced by HPO awardees, although they may also have a presence in HPO-covered regions to provide additional support for clinic visits. Targeted outreach materials will be developed specifically to reach the DV populations.

5.3 The Support Center

A Support Center will provide assistance on demand – via phone, chat, and email – seven days per week between the hours of 7 a.m. and 10 p.m. ET, excluding federal holidays. Instructions for contacting the Support Center will be posted on the research program website and on the Participant Portal. The Support Center phone number and email will also be listed on marketing and promotional materials.

Anyone can contact the Support Center; however, assistance will be limited to topics covered within the IRB-approved participant-facing content, FAQs, scripts, and the Knowledge Base. No clinical guidance or advice will be given. The Support Center will initially assist in both English and Spanish. All inbound requests will be tracked via an electronic ticketing system to ensure proper escalation, closure, auditing, measurement, and process improvement. We will use this tracking system to prioritize and develop new FAQs and Knowledge Base entries to ensure we are meeting the needs of participants.

The Support Center will record whether the caller is part of an HPO or a DV, the nature of the question or request, and the status of the request to ensure it has been adequately addressed. Callers will have the option to voluntarily provide their name, email address or a preferred phone number, and their state of residence for follow-up.

The Support Center staff will triage requests as follows:

- Tier 1—Handled by Support Center staff using the IRB-approved FAQs and/or Knowledge Base

- Tier 2—Directed to affiliated enrollment sites (HPO or DV) for site-specific response—for example, scheduling blood draws and physical measurements
- Tier 3—Directed to Vibrent for technical topics not addressed in the IRB-approved FAQs and/or Knowledge Base (e.g., technical problems with the website or mobile application)
- Tier 4—Directed to Scripps for topics that are not yet covered in the IRB-approved FAQs and/or Knowledge Base. Tier 4 tickets may include:
 - a. “Escalated issues” that were not satisfactorily responded to via the Support Center supervisor
 - b. Feedback or suggestions (about the research program, marketing, research, technology, etc.)
 - c. New topics that should be added to either the Support Center Knowledge Base and/or added to the FAQs

For Tier 3 and Tier 4 topics, subject matter experts (SMEs) will be called for consultation as needed. These topics will be added to the Knowledge Base. Where applicable and following IRB review and approval, responses may also be added to the FAQs.

Standard quality monitoring will be performed to ensure proper escalation, auditing, measurement, and process improvement.

In the future, we will explore whether the Support Center can facilitate the enrollment process for interested individuals lacking digital access or acumen.

5.4 Outreach to Communities

Outreach to communities and grassroots community engagement is foundational to the *All of Us* Research Program. To that end, we are building a national network of community organizations that will facilitate the four essential and unique components of the creation of active participant community: outreach, engagement, recruitment, and retention. We define outreach as providing materials and information to an audience (unidirectional interaction); engagement as listening, responding, and supporting that audience (bidirectional interaction); recruitment as facilitating enrollment in the program; and retention as ongoing activities with participants after enrollment.

There are three members of this national network that will be central to working with communities: Community Partners, Gateway organizations, and the National Library of Medicine (NLM). Each of these three groups understands their communities and will provide outreach, engagement, recruitment, and retention strategies tailored to their communities.

The *All of Us* Research Program enhanced its engagement activities with four inaugural Community Partner awards in FY 2017. These Community Partners now serve as trusted intermediaries, fuel the diversity engine (i.e., enhance the reach of the program to traditionally underrepresented communities), and work collaboratively with the consortium to achieve full engagement and retention of individuals and communities that have been traditionally underrepresented in biomedical research. The inaugural Community Partners are raising awareness about the program among seniors and older adults in rural areas, Hispanics and Latinos, African Americans, and the LGBTQ community to complement

other outreach efforts of the program.

Community Partners use a variety of outreach techniques that include digital (social media, emails) as well as mass-media (broadcast media, printed materials) strategies. For engagement, Community Partners will be utilizing in-person strategies to conduct dialogues with their communities (create advisory councils, educational webinars, and health helplines, as well as tabling). For recruitment, Community Partners will assist interested members of their communities in enrollment (launch events geared towards enrollment, provide enrollment materials at existing events). For retention, Community Partners will show that the program is invested in responding to participants' interests and needs and seeks to work with them for a decade or more (offer regular "check-ins" via phone, ongoing social media campaigns, newsletters).

We are also partnering with Gateway organizations to enhance our community outreach and engagement efforts. Gateway organizations are defined as trusted, grassroots community and provider organizations that, if aligned with the *All of Us* Research Program, can serve as impactful ambassadors, catalyze interest, and pave the way for other organizations to sign on to support the program. Gateway organizations provide many of the same outreach, engagement, recruitment, and retention strategies as Community Partners but also strengthen the support system of respected community leaders (develop train-the-trainer modules, identify and train community/provider leaders in AoURP specifics, develop AoURP specific Continuing Medical Education/Continuing Nursing Education, encourage leaders to provide articles/content for news outlets, provide print materials at local offices).

As another means of outreach to communities and meeting them where they are, the AoURP has formed a creative and innovative partnership with the National Library of Medicine (NLM) to leverage the library system as a respected health resource, convener, trusted intermediary, and resource. For many people in this country, particularly those with limited internet access, the public library system serves as an invaluable and vital community hub. This partnership will focus on three key areas: (1) positioning public libraries to deliver effective community education and awareness for AoURP; (2) AoURP community engagement through public libraries; and (3) the creation of a learning management system platform (LMS). The first area entails distributing AoURP materials (physical signage, handouts and displays) in libraries, providing online health information training for library staff to meet the needs of community members, and creating a traveling exhibit that combines physical displays with interactive public events modeled after the NLM History of Medicine traveling exhibit program. The second area entails establishing a National Network of Libraries of Medicine (NNLM) Program Partner for each of the 8 NNLM regions across the United States that will coordinate AoURP engagement activities with the NLM, pilot and model unique community engagement activities such as training library patrons to reach out to their communities, creating "office hours" at partner locations, providing AoURP materials in bookmobiles equipped with internet access, partnering with other community organizations, and leveraging existing health programming such as maker spaces (do-it-yourself spaces where people can gather to create, invent, and learn) and digital commons in public libraries. Collectively, the information we gather will help us identify best practices for messaging and conduct outreach that leads to increased public interest and engagement in the *All of Us* Research Program. The third area entails creating an online platform and central repository for

educational and training material about *All of Us* and precision medicine, with resources designed for members of the public, health professionals, librarians, researchers, and *All of Us* staff.

5.5 Mobile Engagement Asset

As additional outreach, the *All of Us* Research Program has deployed a mobile engagement asset (MEA) to bring awareness about the research program to remote areas and geographic locations whose residents are traditionally underrepresented in biomedical research. By bringing information about the *All of Us* Research Program directly to these populations, the aim is to break down barriers to equitable representation within the program. This outreach is especially valuable for engaging highly mobile populations like migrant workers and those living in shelters and other temporary housing, racial and ethnic minorities, and the LGBTQ and disability communities. The MEA offers personal exploratory interactions with the *All of Us* Research Program; special attention will be given to creating a warm and welcoming, but not coercive, environment where people can learn about the research program. The MEA experience is carefully developed to be considerate of cultural aspects and to leverage existing community network relationships. The MEA is an agile tool that can be leveraged for other uses when not scheduled for outreach to underrepresented populations. Other uses include support of HPOs and DV partner activity. Community and faith-based groups, consortium members, and other partners can request the MEA through an online event request form found on the *All of Us* website (<http://joinallofus.org>).

Taken together, this diverse set of outreach activities will enable us to significantly amplify the program's messaging through multiple channels and activities across the nation and build a rich and vast network of influencers and community ambassadors to reach, educate, and motivate UBR populations across the nation to enroll and meaningfully engage in the AoURP for the duration of the program.

5.6 Readability of Outreach and Enrollment Materials

Consistent with best practice recommendations of the National Quality Forum (NQF) and the Agency for Healthcare Research and Quality (AHRQ) for engaging participants with a broad spectrum of health literacy, outreach and enrollment materials have been written at the middle-school-grade reading level. This practice ensures that these materials are broadly comprehensible by the greatest number of residents of the United States.

Reading level experts reviewed all public research program copy and assessed reading levels using both the Flesch Reading Ease and the Flesch–Kincaid Grade Level scales. Materials were further reviewed for sentences per paragraph; words per sentence; overall word, sentence, and paragraph counts; and use of passive voice. By adjusting the vocabulary used and the length and structure of sentences and paragraphs, reviewers worked to increase reading ease and reduce grade level. Whenever possible, the amount of copy was reduced while retaining appropriate sentence structure (e.g., no single-word sentences). Finally, reviewers converted copy to the active voice to increase its accessibility and ability to engage low-literacy readers. Following analysis, the research program copy was re-reviewed to ensure that essential meanings and concepts were fully retained. The target metrics are:

Flesch Reading Ease: ≥ 70

Flesch-Kincaid Grade level: ≤ 7

Passive sentences % of total $\leq 10\%$

Sentences per paragraph: < 3

Further, where possible, the enrollment materials incorporate multimodality presentation methods (aural, visual, and interactive) to aid comprehension of persons with low literacy. For example, animated videos with visual cues and voice modulation will further facilitate comprehension in low-literacy populations. For people who wish to read more in-depth information, some information on a limited number of key topics may be written at a high school or college reading level.

6 Enrollment

Enrollment in the *All of Us* Research Program is voluntary and not time-sensitive.

6.1 Levels of Enrollment

There are four levels of participation for internal tracking:

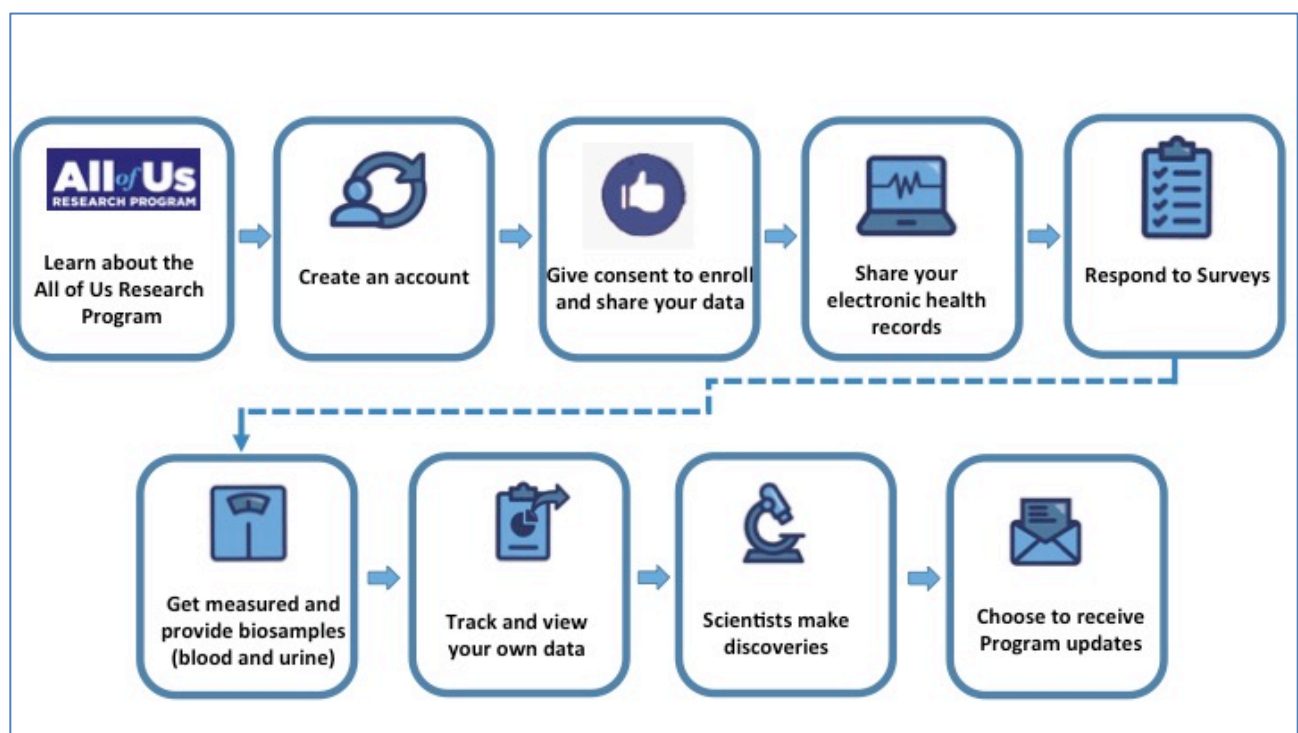
- **Interested individual:** Someone who provides contact information to receive research program updates. This person may have downloaded the research program app and/or pressed “Join Now” on the website.
- **Registered individual:** A person who created an account by entering a name and email address and has chosen a language preference but has not yet completed the informed consent process. A registered participant has a unique AoURP participant identifier (PID).
- **Consented individual:** A person who meets the eligibility and inclusion criteria and is enrolled in the *All of Us* Research Program. A consented individual has completed the primary informed consent process and the HIPAA Authorization/EHR consent (if available and where relevant, based on AoURP capacity to effectively search for and access records). A consented individual hasn’t yet participated in any research program activities such as completion of questionnaires or providing physical measurements and biospecimens.
- **Participant:** A person who completed “The Basics” PPI module and who is in the eligibility queue for providing physical measurements and biospecimens.
 - **Core Participant:** A person who completed the required PPI modules and provided physical measurements and biospecimens. A core participant can contribute to other activities such as providing digital health data using sensor modules and/or wearables, if available.
 - **Active Participant:** A participant who accessed the Participant Portal and has completed at least one AoURP activity in the past six months.
 - **Full Participant:** Someone who completes all protocol elements available to them over the life of the program.

We will track participant enrollment levels over time and report back to the Steering Committee and NIH on our success against ongoing targets for diversity and inclusion in the program.

Anyone can access the full complement of outreach and enrollment materials, including templates of informed consent documents, through the research program website or through the web mobile application. The web application will be compatible with modern major browsers. The mobile application will be available free of charge for iOS operating systems within the Apple App Store and for the Android operating system on the Google Play marketplace. Prior to download, individuals may review a high-level description of the research program posted on the Apple App Store and Google Play marketplace. After downloading, individuals can review educational content about the research program within the mobile application.

The Journey through the *All of Us* Research Program is summarily illustrated in Figure 6–1: Participant Journey.

Figure 6–1: Participant Journey



Note that DV enrollees who are not in a state supported by an HPO will not be asked to share their EHR until the technology to acquire their EHR is in place. Instead, they will be shown a few screens about the value of EHR information to the program and asked if they would consider sharing access to their EHRs in the future if we have a mechanism to collect them.

Recognizing that individuals may not have their own device for accessing these materials, HPO sites may provide tablets, wired computers, laptops, and/or smartphones pre-loaded with the relevant materials to consult on site.

6.2 Account Creation

Account creation begins with the interested individual clicking the “Join Now” button on the website or mobile application. Account creation requires entering one’s first and last name and an email address, creating a password and confirming it, and choosing a preferred language from a drop-down menu. AoURP is working to deploy a variant that will enable using one’s phone number rather than an email address for account creation.

As with other information containing personal identifiers, this contact information will be stored securely in the Raw Data Repository (RDR). Access to the participant’s account information will be available only to a select number of trained program staff for data validation and regulatory purposes. The DRC will generate a unique internal participant identification code, represented as a random 10-character string (format P000000000) that is used to access participant information without using explicit personal identifiers.

Individuals must create their own accounts themselves but can be assisted by a trained program staff by phone through the Support Center or in person at an HPO site. Currently, all individuals will create their account electronically. We recognize this limits participation for some individuals and could impact diversity and inclusion within some communities. As stated earlier, a plan to accommodate individuals with differing levels of technological capability is to be developed and subsequently submitted to the IRB.

Accounts can be created using the web application interface or through the dedicated mobile application.

6.3 Information Collected Prior to Informed Consent

Following account creation, persons wishing to enroll in the program will need to answer the following questions in advance of providing informed consent:

- They will be asked to confirm they meet each of the eligibility criteria (e.g., Are you age 18 or older?)
- They will be asked their state of residence and the state where they receive most of their health care. This enables compliance with state-specific requirements, such as disclosure of the California Experimental Bill of Rights to individuals residing in California.
- They will be asked if they are members of any of the research program affiliates within their state of residence or the state where they receive most of their health care. This enables pairing the individual to a partner site that is most convenient for them. This also allows customization of the app based on specific sites’ readiness and preferences.

This information will be collected and used for the purposes described above.

6.4 Informed Consent Overview

Informed consent of participants is fundamental to the ethical practice of human subjects research. Disclosure, voluntariness, and decisional capacity make up the core of valid informed consent processes.

All persons wishing to participate in the *All of Us* Research Program will complete an informed consent process. Through this process, participants will unambiguously indicate

their consent to join using IRB-approved text and visual aids (including video). The materials presented will be consistent across the research program but may be customized based on an individual's geographic location, enrollment method, or affiliation (DV or HPO).

The informed consent process will initially be administered and documented electronically. It is designed as a living process, with information loops and opportunities for periodic updates. The electronic consent process is self-paced, and there is no time limit to complete it. Individuals can rapidly navigate, repeat, pause, and review according to their own information needs. They can easily navigate between the informed consent process and learning more about topics of interest through the research program website, or they can contact the Support Center. Telephone and electronic chat support are available for all; those enrolling on site may also have access to informed consent facilitators for in-person exploration of topics of interest. The consent process can be experienced as a self-navigated, staff-supported, or hybrid process. Individuals will be able to choose their preferred informed consent experience by (a) self-navigating the consent process through the web or mobile research program application, (b) soliciting support from trained staff at either an HPO site, or (c) calling the Support Center.

Only trained program staff will be able to offer support to individuals with technical/computer issues, literacy issues, and/or questions during the consent process. This approach helps to ensure consistency between enrolling centers as well as ensuring that an individual's decisional autonomy is respected.

Informed consent materials will be available in English and Spanish at launch and in additional languages thereafter. Translated materials will be generated through an IRB-approved translation procedure and provided to the IRB for their records. Verbal translation into languages without official translation will not be allowed.

Any awardee institution wishing to use approaches to informed consent other than those described here will submit their site-specific plans to the IRB as part of the Institution-Specific IRB Application (ISIA).

6.4.1 Considerations for On-Site Enrollment

Individuals who are enrolled at an HPO site will be provided information on how to download the mobile app and/or navigate to the web application. An on-site kiosk or tablet/iPad may be available at some locations to review the eConsent and audiovisual content.

Interested individuals will be clearly informed that their decision to participate in the research program will not impact the care they will receive. Program staff will be trained to approach only individuals who are stable, coherent, and able to carry on a conversation freely.

6.4.2 Additional Modalities of Consent

To ensure the accessibility, inclusivity, and diversity of the research program, the current electronic informed consent process will be adapted to meet the presentation needs of

variable learning styles and health literacy levels. These plans include a video-only consent, a paper-based consent process, and the incorporation of kinetic elements into the consent process to aid comprehension and support autonomous decision. These procedures will serve those with low technology proficiency and/or without access to an online infrastructure and/or other preference or challenge that prohibits enrollment via the electronic process. These additional modalities of consent do not preclude person-to-person contact for questions and/or concerns. Trained personnel are available on site and at the Support Center to address questions or concerns about the program.

Regardless of the approach to consent, individuals will be registered through the mobile application (app) or research program website with their email address (or phone number once the functionality is available). This can be accomplished with the help of trained program staff using on-site computers and/or mobile technology. Participants will be given access or receive a copy of the consent form for their records. Future contact from the research program will use the phone number and/or email address that was used to register their account.

6.4.3 Facilitated Consent

As previously described, the consent process may be self-navigated or completed with staff support. There are circumstances where a staff-facilitated consent process may be utilized, depending on the participant's physical, social, educational, or other limitations or preferences that necessitate this approach to meeting their needs as an individual. For example, facilitated consent will be offered to persons who are visually impaired until an audio-only consent process is enabled. Trained program staff experienced in facilitating standard informed consent procedures will be available to facilitate review of consent materials with individuals in such cases. Trained program staff members will utilize approved electronic consent visual aids and text during this process and will engage the participant in a discussion of informed consent to answer any additional questions or concerns a participant may have. In cases of facilitated consent, the facilitator will be required to co-sign the informed consent document.

The Support Center will also have a standardized procedure for a fully facilitated consent process; a separate amendment will be submitted for IRB approval at that time.

6.5 **Electronic Consent**

At first, an electronic informed consent process is to be used for all *All of Us* Research Program participants (at HPOs or DV partners) to ensure consistency and standardize the consent information. This strategy was also selected to allow for rapid scaling of consent. The electronic consent process serves as an aid to understanding the core elements of the research program. It includes information on the detailed nature, purpose, procedures, benefits, and risks of and alternatives to participating in the *All of Us* Research Program.

Due to the longitudinal nature of the study and the patchwork of state regulations regarding research – and to provide a flexible participant experience – the informed consent for the *All of Us* Research Program is modular. Each module requires an electronic signature from the participant:

1. *Primary Consent*: The primary consent module gives an overview of all program activities. Signing the primary consent indicates general understanding of the research program and approval to take part in the PPI, Data Linkage, Physical Measurements, Biospecimen Collection, Biobanking, Biomarker assays, Genomic Testing, and Sensor/Wearable Technology activities if invited.
2. *HIPAA Authorization for Research EHR/Part 2 Supplement*: This module gives details about allowing the research program access to a participant's electronic health records, including health records protected by 42 CFR Part 2 (drug and alcohol abuse patient records), referred to as "Part 2" records. State-specific versions of this form are developed as needed to meet state regulations regarding the release and use of health record data.
3. *Return of Genomic Results (ROGR)*: This module, which is currently in development, will explain the potential risks and benefits from receiving genetic/genomic results from the program. It is anticipated that variations on this module will be required to satisfy state-specific regulations regarding the return of genetic/genomic results, although all efforts will be made to keep the consent process as consistent as possible.

Note that while the program seeks to deploy a primary consent that includes consent for genomic testing, such testing will not be initiated without prior implementation of the ROGR module. This will ensure that individuals' genomic data can be returned to them before or simultaneously with its availability to users of the *All of Us* Data Resource.

Each module is comprised of three information-giving components:

1. eConsent screens
2. Formative evaluation
3. Form requiring signature

The modules can be arranged to meet the needs of member organizations with local populations in various states of readiness while also providing consistent, multimodal informing content to participants.

6.5.1 eConsent Screens

The eConsent screens present key ethical concepts through a set of visual icons, short videos, and concise, highly structured text blocks. The development of the eConsent screens is informed by electronic consent design literature and formatting principles. These formatting principles aim to deepen participant attention and facilitate comprehension, especially for participants who are self-administering consent.

The videos associated with the eConsent facilitate elaboration on key aspects of the research program without increasing reader burden for those of low literacy or those who learn best from non-text-based presentation of information. Brief audiovisual segments describe elements of research program participation, such as answering health questions, being measured, or giving samples, as well as data sharing and privacy. Each segment will play when the person navigates to the appropriate eConsent screen. The person will

not be able to navigate forward until that video segment is complete, ensuring a more uniform informing experience for all participants.

Consistent with the design of the modular consent, there are three core eConsent screen sets:

- Primary eConsent Screens. Present an overview of the *All of Us* Research Program and information on all procedures and aspects of participation.
- HIPAA Authorization for Research EHR/Part 2 Supplement eConsent Screens. Present a more detailed look at EHR/Part 2 data donation, including scope, limits, risks, and benefits.
- Return of Genomic Results (ROGR) eConsent Screens (in preparation). Will present a more detailed look at the return of genetic/genomic results, including scope, limits, risks, and benefits.

Additionally, to mitigate informedness decay over time, there are two eConsent “refresher loop” screen sets:

- Physical Measurement and Biospecimen Refresher eConsent Screens. For participants for whom physical measurement and biospecimen donation is separated in time from the primary eConsent, this refresher will remind participants of the scope, limits, risks, and benefits of these procedures.
- Sensor and Wearable Technology eConsent Screens (in preparation). Will present a more detailed look at sensor/wearable technology participation, including scope and limits. These screens will specifically address the reasons for the collection of this data, as well as distinguishing between the baseline privacy and confidentiality risks of using sensors and any additional risk from their use in the *All of Us* Research Program. Participants may be able to designate what data is collected from their devices as part of participation.

To further enhance transparency and enable autonomy, near the end of each of the eConsent modules (Primary Consent, HIPAA Authorization for Research EHR/Part 2 Supplement, and Return of Genomic Results) – and after viewing the related consent forms – participants will be required to complete a brief formative evaluation prior to being able to electronically sign the consent form and thereby complete a consenting interaction. A formative approach was chosen to reinforce key concepts and specifically target common misconceptions in human subjects research (e.g., therapeutic misconception). Topics included in the formative evaluations have been informed by existing empirical research (Beskow et al., 2015).

As each question is presented, individuals are asked to choose between two response options. Following their selection, individuals will receive immediate feedback on whether they have answered correctly or incorrectly. An educational reinforcing screen will be presented back to all individuals, regardless of correct or incorrect response. Individuals answering incorrectly will not be penalized. This format is designed to create an opportunity for pauses and repeated promotion of key concepts to prospective participants. At the end of the formative evaluation, the number of correct answers out of the total number of questions is presented. Individuals are then able to self-assess and self-determine their next step: Navigate onward to sign the consent form, revisit consent materials, or seek additional support. Participants enrolling at an HPO enrollment site will have the option to ask trained program staff at the site for assistance. Both HPOs and DV

participants will also have the option to contact the Support Center for assistance. This formative approach supports participant informedness prior to consent and serves as a check on a participant's understanding, especially for those participants self-administering consent.

6.5.2 Consent Form and Supplements Requiring Signature

To meet regulatory requirements, a primary informed consent form and a HIPAA Authorization for Research EHR/Part 2 Supplement form have been drafted. Another supplemental form describing the return of genetic/genomic results will be developed. These forms will be readily available for review through the *All of Us* Research Program website and through the app without any registration for access. Each form will be presented to participants following the related eConsent screen set. Participants will electronically sign these forms using either their finger on a touch screen, using a computer mouse, or typing into an electronic text box and completing their profile. They will receive a PDF version of their signed consent document by email or in printed form from program staff at the time of an in-person visit if requested. They may also view, download, or print the document from their account at any time.

The participant's signature at the end of the primary consent form indicates that the person is consenting to PPI and data linkage. Additionally, this form documents consent for physical measurements, biospecimen collection, biobanking and genomic analysis, and sensor or wearable technology data collection, should that person be invited and choose to participate in those modules of the *All of Us* Research Program. A signature on any consent document does not constitute a "contract" of promised data donation by the person nor that the research program will invite that person to any specific part of the research program

A signature on the HIPAA Authorization for Research EHR/Part 2 Supplement form is required for release of electronic health records and Part 2 health record data. Participants can revoke their HIPAA Authorization for Research EHR/Part 2 Supplement consent at any time and for any reason, without leaving the program. Like their authorization, their revocation modality may vary per state regulation (for example, whether it requires a witness). Another signed consent supplement will be required to authorize the return of genetic/genomic results. This consent supplement form for return of genetic/genomic results is currently under development and will undergo legal review for compliance with the diverse state regulations governing return of genetic/genomic results in research prior to submission to the IRB.

Participants may be required to sign additional documents (e.g., the California Experimental Subject's Bill of Rights), as mandated by state law.

Because the primary consent form and any supplement will contain personal identifiers, these forms will be kept separate from the data in the *All of Us* Research Program Research Portal that will be queried and analyzed by researchers. The signed consent forms' data will be stored in the Participant Portal database, and copies of the signed informed consent forms will be stored securely in the Raw Data Repository, like other forms containing personal identifiers. Access to this data will be available to trained

program staff via HealthPro for management purposes and for data validation and regulatory purposes.

6.5.3 Refresher Loops

Due to the longitudinal nature of the cohort and to recognize that informed consent is not a discrete process but a long-term engagement between participants and researchers, the *All of Us* Research Program will include “refresher loops” to guard against informedness-decay. These refresher loops will be eConsent screens, or similar modalities, and designed to reinforce key concepts, especially for research program activities that may be separated in time from the primary consent module. There will be a physical measurement/biospecimen refresher loop and a sensor/wearable technology refresher loop (in planning). Additional refresher loops will be developed over time, depending on participant and research needs.

6.6 Data Oversight and Choice of Law

The considerable number of distinct state laws and regulations governing the collection and use of various data types collected by the research program have prompted the *All of Us* Research Program to seek guidance from the NIH Office of General Counsel and the Office of Civil Rights. These offices will provide recommendations on the appropriate application of state regulation in the context of this national research program. This consultation is especially important given the long duration of the study, along with the well-documented mobility of the United States population and, specifically, the higher mobility of those who are poor and non-white (U.S. Census Bureau CB 16-189). Further, the program will involve populations traditionally underrepresented in biomedical research who have exceptionally high mobility, including migrant workers, the homeless, and gender and sexual minorities. Understanding of these state-by-state variations will be essential to meeting our ethical obligations to mobile populations. The research program will use this guidance in revisions of participant materials, consent, and workflow for all future submissions.

7 What Is Involved? Program Procedures

Once an individual has confirmed their decision to join the *All of Us* Research Program by completing the informed consent process, that person is eligible to start contributing information to the program.

Since some participants may complete the consent process and one or more PPI questionnaires online prior to being invited to a clinic visit at an HPO or DV site, trained program staff will follow site-specific policies and procedures to confirm the participant’s identity (confirmation of name and contact information, photo ID, etc.) at the beginning of their appointment and confirm that the participant wishes to move forward with study procedures listed in the consent document. The process for confirming identity at each site is defined in the site-specific ISIAs.

The time to complete the participant journey in one setting ranges between one and three hours (excluding time required for consent). As noted above, some participants may complete certain PPI modules ahead of time; therefore, the time required in one setting

may be significantly less than two hours (Table 7–1: Estimated Duration of Participant Journey). These times are not intended to reflect time for transportation to the site or wait times prior to initiation of data collection.

Table 7–1: Estimated Duration of Participant Journey

Domain	Description of Content	Duration
Enrollment	Create account via website or mobile application	5–10 minutes
Informed Consent	From website or mobile application: <ul style="list-style-type: none"> • View primary eConsent screens • Review primary consent form • Complete primary formative evaluation • Sign primary consent form • As appropriate, view refresher loops and/or complete additional consent modules 	Primary: 15–45 minutes Additional informing content: 5–15 minutes
Participant-Provided Information	<ul style="list-style-type: none"> • Basics (sociodemographic information) • Overall health • Lifestyle (personal habits) • Personal medical history* • Medications* • Family medical history* • Health care access and utilization* 	5–20 minutes each (see below, Table 7–3)
Check-In	<ul style="list-style-type: none"> • Verify address or key personal information • Verify consent is e-signed before visit • Summarize what to expect of the visit; answer any questions • Instruct participant to remove bulky clothing 	5–10 minutes
Pre-Measurement Verifications	<ul style="list-style-type: none"> • Verify completion of PPI • Collect limited information relevant to the measurements and biospecimen collection (e.g., what time did the person last eat anything?) 	5–10 minutes
Physical Measurements	<ul style="list-style-type: none"> • Sit for 5 minutes • Conduct program core physical measurements, to include: <ul style="list-style-type: none"> ○ Blood pressure and pulse—6 minutes ○ Height and weight—3 minutes ○ Hip and waist circumference—2 minutes 	15–20 minutes
Biospecimen Collection	<ul style="list-style-type: none"> • Perform blood draw • Collect urine specimens • Collect saliva samples instead of blood (optional) 	10–45 minutes
Check-Out	<ul style="list-style-type: none"> • Verify the completion of measurements and biospecimen collection • Provide printout and/or digital measurement data, as well as results, to the participant • Discuss what to expect post-visit, and answer any questions 	5–15 minutes

* PPI in preparation

7.1 Participant-Provided Information (PPI)

In addition to contact information and data for creating an account, the program plans to obtain extensive information about a participant’s health status through self-completed surveys. This participant-provided information (PPI) will include data relevant and

necessary for scientific research studies (e.g., personal and family medical history, socioeconomic factors, and health care access and utilization).

Most questions will be selected, or modified, from various health-focused surveys previously validated in large cohorts and cross-sectional studies (e.g., the National Health and Nutrition Examination Survey [NHANES], the National Health Interview Survey [NHIS], the Behavioral Risk Factor Surveillance System [BRFSS], the Million Veteran Program, and UK Biobank). Throughout the program, new modules will be developed in the English language via a dedicated Participant Provided Information Committee and expert task forces for each prioritized content area. The questions will be further refined through testing using standard cognitive interviews and online user assessment. This phase also enables exploration of the understandability of the survey, accuracy of responses among members of diverse groups, and identification of gaps in survey coverage of issues important to participants. The IRB-approved English-language versions of survey modules will be translated in other languages, starting with Spanish, using the IRB-approved translation procedure. All translated modules will be tested in each language.

7.1.1 PPI Readability Analysis

Consistent with the guiding principles of the program, each PPI is assessed for readability using the Flesch–Kincaid Grade Level scale and refined by reading-level experts to ensure it is broadly comprehensible by the greatest number of residents of the United States. Questions are edited where needed to improve readability and clarity, in line with current best practices to use language at the fifth- to sixth-grade reading level. Additional directions and concept explanations are also added to complement question-and-response options as needed to improve clarity. Following readability analysis, each PPI is re-reviewed to ensure that essential meanings and concepts are fully retained.

There are three surveys available to participants at baseline: The Basics, Lifestyle, and Overall Health. Prior to the physical measurements and biospecimen collection, participants may complete these three self-administered questionnaires. Participants will be able to save their answers and return to complete each survey later if needed. On average, it takes about 10 minutes at the median and about 30 minutes at the longest to complete (Table 7–2: Survey Completion Times).

Table 7–2: Survey Completion Times

The <i>All of Us</i> Research Program Survey	Average (min:sec)	Median (min:sec)	Range (min:sec)
The Basics	8:11	6:30	2:00–17:51
Lifestyle	3:23	1:23	0:17–7:05
Overall Health	3:10	2:00	0:14–6:06
Personal Medical History	11:23	9:20	2:24–25:23
Family Medical History	10:15	9:52	0:08–37:19
Health Care Access and Utilization	21:36	20:02	7:59–46:45

Participants will be invited to complete additional surveys about their health throughout the duration of their participation. The next 3 modules to be offered after IRB approval include Personal Medical History, Family Medical History, and Health Care Access and Utilization. Surveys in domains such as Diet, Physical Activity, Medications, Environmental Exposures, Mental Health, and Sleep are also planned. They will be developed on an

ongoing basis and will be submitted to the IRB for review and approval prior to implementation.

7.2 Use of Personal Health Technologies

Data from sensors and software applications can give researchers a clearer view into health-influencing factors and health-related outcomes that have previously been difficult to capture with accuracy. Digital health technologies can offer unique advantages to both participants and researchers. Some technologies **passively collect data**, which produces minimal participant burden and avoids biases related to retrospective self-reporting. Technologies that interactively collect data are nonetheless **controlled by the participant** and are often used in a participant's normal environment. Both passive and active modalities collect data independent of clinical or technical staff and thus lower the threshold for allowing participants to share frequent and longitudinal measurements.

It is anticipated that, throughout the life of the program, an array of sensor technologies will enable the longitudinal collection of physiologic and environmental data. Some of these sensors are already built into smartphones, such as those that can measure motion, sound, or visual data like nutritional barcodes. Others will include wearable sensors, including but not limited to wristbands and watches that can measure activity, sleep quality, heart rate, and respiration. Additional sensor technologies may include those placed within a participant's residence or automobile that can passively monitor environmental parameters such as temperature and air quality and track a variety of biometrics. As these technologies continue to evolve, it is anticipated that many more factors that influence health will be monitored.

7.3 Physical Measurements

Participants will have a standardized set of physical measurements collected and recorded in HealthPro. The same core set of baseline measurements will be carried out irrespective of enrollment through an HPO or as a DV.

The inclusion and exclusion of specific measurements as part of the baseline physical measurements were determined based on their potential relevance to research, widespread reproducibility in all enrollment settings, the time and training requirements needed to carry them out appropriately, and the resources required to obtain them. In total, it is anticipated that the components to be included in the baseline physical measurements will require 15 to 20 minutes to complete.

In some circumstances, a home visit by a trained program staff member may be necessary to enable the physical measurements.

The baseline physical measurements will include physiologic (e.g., blood pressure and heart rate) as well as anthropometric (e.g., height, weight, waist and hip circumference) measurements. Body mass index will be calculated automatically from measured height and weight. Obtaining these physical measurements will confer minimal risk to study participants, as outlined in Section 8 (Risks/Benefits Assessment).

The trained program staff member conducting the measurements will record the information on a dedicated HealthPro platform. Participants will have access to their physical measurements through the Participant Portal. In addition, if they wish, participants will receive their physical measurements in writing before they leave the HPO/DV site.

Trained staff will be notified immediately upon entering of any measurements that are deemed actionable based on deviation from population norms in HealthPro. HealthPro will provide clear guidance to trained staff regarding next steps, including referral for additional evaluation. See Section 10, Access to Individual-Level Information for Participants, for additional details.

7.4 Biospecimen Collection

Understanding the relationships between circulating biomarkers or genetic variation as they relate to disease prevention is a primary aim of the *All of Us* Research Program. The objective of the program regarding biospecimens is to collect samples that would allow the broadest range of clinical and research assays that could reasonably be envisioned for the future and to avoid collection, processing, or storage approaches that would inherently preclude such assays.

The Biobank will be responsible for working with the DRC and HPO/DV sites to develop standard operating procedures and kits for the collection, initial processing, and transfer of the biospecimen to the Biobank. Initially, adult participants may provide up to 50 mL of blood and 50 mL of urine. In cases where it may not be possible to obtain a blood sample, a saliva sample may be collected instead for the purposes of isolating DNA.

It may be necessary to modify the sample collection protocol to enable new scientific opportunities. Any change that is within the 50-mL threshold for either blood or urine collection will be implemented once the infrastructures for the change are in place. Sites may convert to a new sample collection protocol on a rolling basis over time. Therefore, there may be times when more than one version of the sample collection is effective across AoURP. Updated records of sample collection protocols and the types of sample collection tubes will be provided to the IRB. Changes that increase the blood or urine collection volume above 50 mL or add new sample types will be submitted to the IRB for review and approval prior to implementation.

For individuals who enroll via designated HPOs, the physical measurement and biospecimen collection visit may occur at the initial enrollment visit, following consent and completion of the sociodemographic PPI module (The Basics). Individuals who enroll remotely will travel to a designated HPO or DV partner facility of their choice for their clinic visit. In some circumstances, a home visit may be necessary (e.g., individuals who report limited mobility, whose health prevents commuting, and those who live in an area where there is no DV partner site within a reasonable distance).

7.4.1 General Approach to Sample Collection

The Biobank procedures included in a separate Manual of Procedures specify the samples to be collected, the preprocessing requirements, shipping temperatures, the transport of samples to the Biobank, and the processing, aliquoting, and storage of each sample type.

For the blood collection:

1. The amount of blood collected from healthy, non-pregnant adults who weigh at least 110 pounds may not exceed 550 mL in an 8-week period, and collection may not occur more frequently than 2 times per week.
2. The amount of blood collected from other adults and children may not exceed the lesser of 50 mL or 3 mL per kg in an 8-week period, and collection may not occur more frequently than 2 times per week.
3. The maximum number of needle sticks by the phlebotomist is three. If unsuccessful after the first two needle sticks, and only with the consent of the participant, one additional attempt will be made, ideally with a new phlebotomist.
4. If the first collection attempt is not successful, the participant may schedule an additional visit to complete the biospecimen collection.
5. If the sample collection is not successful after two attempts, or if the participant is not able to return for a second visit, the phlebotomist will propose to collect a saliva sample for DNA.

If the minimum blood draw of a 4-mL EDTA tube is successfully drawn, the blood draw will be considered successful and saliva will not be sought.

The participant's health and the total volume of blood drawn on any single day need to be considered. Recognizing that some participants could be recruited from outpatient HPO sites where other specimen collections may occur for standard of care, ambulatory participants who are healthy or in stable medical condition should not have more than 200 mL of blood drawn in a single day.

Table 7–3: Questions to Participants Prior to Scheduling the Blood Sample Collection

Question to ask participant	If answer is “yes”	If answer is “no”
In the past week have you donated blood (e.g., to a blood bank or Red Cross), platelets, or plasma?	Participant will need to schedule their biospecimen collection at least five days past the initial donation date	Research specimen collection to occur as normal
In the past six months, have you had a blood transfusion?*	Participant will need to schedule their biospecimen collection at least six months past the initial date of blood transfusion	Research specimen collection to occur as normal

*Blood transfusion excludes other blood products, such as platelets and plasma.

To address this issue, along with concerns around potential contamination, participants will be asked a series of questions pertaining to blood draw and transfusion at three distinct times: at the time of registration, during scheduling, and immediately prior to blood draw. Based on the participant's responses, trained program staff will then adhere to the procedures described in site-specific Policies and Procedures (Table 7–3: Questions to Participants Prior to scheduling the Blood Sample Collection). Potential risks to the participant are expected to be minimal, as outlined in Section 8, Risks/Benefits Assessment.

7.5 Biospecimen Processing and Storage

Biospecimens will be shipped to Mayo Medical Laboratories (MML) for initial unpacking, accessioning, and sorting. They will be processed and stored in the centralized Biobank at Mayo Clinic. Samples will be held at the centralized Biobank indefinitely unless an individual participant withdraws from the study.

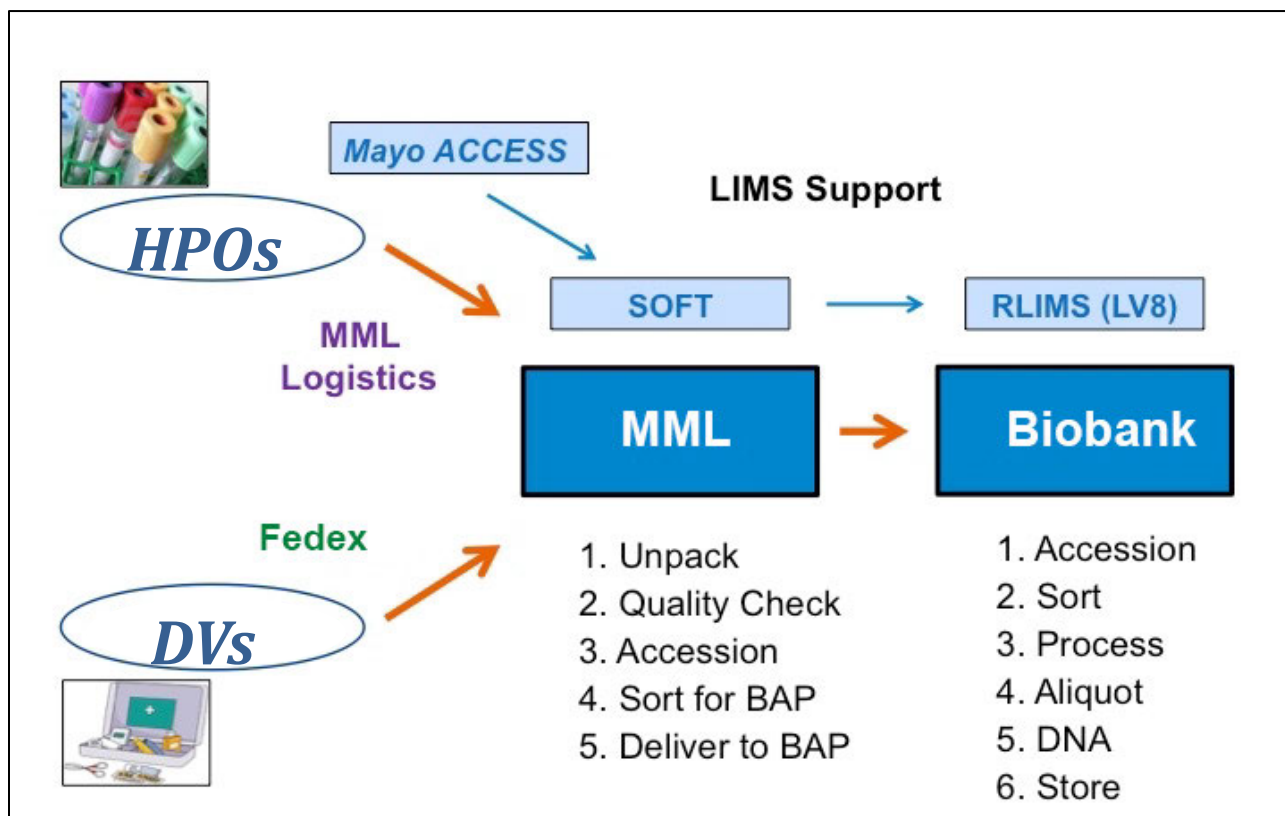
The centralized Biobank will be responsible for facilitating collection, shipment, processing, DNA isolation, sample aliquoting, storage, and future access to biospecimens. Initial sampling processing will be performed at the site of collection followed by a shipping protocol that maintains the cold chain needed to prevent specimen degradation.

7.5.1 Processing Methodology

The collection site will perform minimal sample processing as described in the Biobank standard operating procedures. All specimens will be stored refrigerated until shipped. Specimens will be shipped to the Biobank within 24 hours of collection and processed by the Biobank within 40 hours. The shipment and processing timeline will be met in all circumstances, including holidays and weekends.

All blood tubes will be processed at the Biobank as described in the Biobank standard operating procedures. Information on all aliquots, including the volume for each, will be recorded in the laboratory information management system and linked to a unique Biobank ID. The unique ID is used to reconcile all specimens recorded in HealthPro and the MML records.

Figure 7–1: Biospecimen Flowchart



Mayo ACCESS—This is proprietary software developed by Mayo Clinic to support sample accessioning at collection sites.

7.5.2 Transport of Biospecimens

All biospecimens will be shipped to Mayo Clinic in Styrofoam containers containing a cool pack to keep samples cool. For HPOs, a Mayo Medical Laboratories (MML) courier will be responsible for the packaging materials and containers, packing samples, and adding the cool packs in the shipping container. The logistic capability provided by MML will be used to transport the specimens from the HPO sites to the Biobank. MML utilizes a network of couriers, coupled with a direct arrangement with FedEx and other carriers, to enable daily domestic and international specimen shipment from clients to the performing laboratories in Minnesota, ensuring that shipments are made in accordance with all federal, state, and international regulations. For DV partner sites, a kit will be provided to all collection sites. The kit includes the supplies required for a complete blood draw and urine collection, including the Styrofoam container, a cool pack, and shipping instructions. Completed kits will be shipped back to Mayo Clinic via FedEx courier.

7.5.3 Reliability of Sample Tracking and Identification

The collection sites will utilize MayoLINK, a Mayo Clinic application that provides connectivity to Mayo Medical Laboratories (MML) to order the participant's biospecimen collection. The Biobank laboratory information management is built on software developed by LabVantage Solutions, Inc. (www.labvantage.com). Core capabilities include kit tracking, sample accessioning and annotation, sample processing and testing, storage,

and shipping. All aspects of the sample lifecycle are tracked. Security within this application is robust and multilayered to keep participant and sample data secure.

The enrollment sites will utilize HealthPro, a web-based application developed and managed by the DRC to record information from participants' physical measurements and to complete the biospecimen ordering workflow. Within HealthPro, authorized and trained program staff will be able to view the first name, last name, date of birth, and zip code of a participant to verify participant identity during the measurements and biospecimen collection. The Biobank ID will also be displayed. Prior to sample collection, a sample manifest and labels for the collection tubes will be printed via the HealthPro Portal. The collection tube labels will contain the unique Biobank ID but no other participant identifiers. The Biobank ID will be linked to the participant ID by the DRC. Security will meet FISMA Moderate Authorization and Accreditation standards.

7.5.4 Sample Receipt, Verification, and Routing

Samples will first be transported to MML. Trained Program Staff will triage incoming shipments by shipment time. Specimens will be taken from their original shipping containers and stabilized at the correct temperatures. The specimens will then be expedited to the internal operations area for order processing and receipt verification before being routed to the Biobank. Operators manage the automation and specimens receipt and processing. The validated transportation temperature is maintained at all times during pre-analytic processes, and specimens will be promptly delivered to the Biobank at the same temperature used for shipping.

7.5.5 Long-Term Specimen Storage

Processed blood samples will be stored in robotically controlled –80°C freezers, and whole blood samples will be stored in vapor phase liquid nitrogen units. Most prepared specimens will be stored at the primary site in Minnesota; the Jacksonville, Florida, Biobank facility will serve as the off-site, secondary storage site for approximately 25% of the samples. Both Biobank sites have a comprehensive disaster recovery and business continuity plan.

7.5.6 Destruction of Biospecimens

Participants in the *All of Us* Research Program may withdraw from the program. In some cases, participants may wish to have stored biospecimens destroyed as part of this process. The procedure for destruction and disposal of biospecimens is outlined in Section 9.4, Destruction of Specimens)

7.6 Electronic Health Records (EHRs)

Participants will be asked to authorize linkage of their EHR information if available. Although such linkage involves moderate risk to a participant's privacy and data confidentiality should the data security protocol be compromised (see Section 8.1, Risks), longitudinal tracking of health outcomes through EHRs is an important component of the *All of Us* Research Program.

EHR data may be sent directly by the participant's health care providers to the DRC or sent by the participant to the program through [Sync for Science](#) (S4S) and/or other vendors. EHR data will be sent to the DRC periodically throughout the life of the program. The initial data types to be included are demographics, visits, diagnoses, procedures, medications, laboratory tests, and vital signs, but will be expanded to all parts of the EHR, including health care provider notes, radiology, messaging, reports, and other testing (e.g., electrocardiograms), if applicable. The feed may include information about mental health, HIV status, substance and alcohol use, and genetic/genomic information stored in the EHR. Participants will need to complete and sign a separate informed consent module per relevant state regulations to authorize access to their EHRs.

We will create an informatics infrastructure to clean and standardize data from disparate EHR systems across the United States; this broadly applicable system will be a key contribution of the *All of Us* Research Program to health informatics research efforts nationwide. For participants enrolled by HPOs, the site will extract data from the participant's EHR, format it according to the DRC's data model (currently based on the Observational Medical Outcomes Partnership [OMOP] Common Data Model version 5 at www.OHDSI.org), and transfer it to the DRC using secure protocols. We will continuously adapt the data models as necessary to accommodate *All of Us* data, such as PPI data.

Although obtaining EHR data from DV participants presents unique challenges, early pilot studies have demonstrated the feasibility of such an approach. For example, the S4S project launched by NIH and the Office of the National Coordinator for Health IT is creating a technology that aims to make it easy and safe for people to securely share their EHR data for research. S4S has been adopted by AoURP and initially will be enabled in a small pilot for DV participants at S4S-enabled DV sites. DV participants who have enrolled at one of these pilot sites will be able to sign into their health care provider's patient portal by using the S4S workflow and authorizing sharing their EHR data with the program. Their health care provider's system will provide a secure application program interface (API), which will be used by the *All of Us* Research Program (rather than the provider sending data out) and transmitted to the DRC.

Important gaps in current methodologies include the ability to acquire EHR information from:

1. HPO enrollees who obtain some of their care outside of the HPO
2. DVs who either do not have an EHR or possess an EHR that is not readily shareable

Ultimately, the goal is to have S4S or other technology available to all participants.

7.7 Data Linkage

Linkage of diverse data streams may enhance the analyzable dataset from a given individual. The *All of Us* Research Program will obtain PPI data, EHR data, physical measurement data, and biospecimen data. Linking these data to additional data sources relevant to the individual may present a more complete picture of the health of the individual.

Most data linkage approaches use common identifiers (e.g., first name, last name, date of birth) to uniquely associate information from various sources from a given person. Algorithms for deciding if one person is the same as another can be either deterministic (i.e., exact match) or probabilistic (likelihood of match). Use of identifiers in a human-readable form is referred to as “clear text” linkage method. Most current data linkages in health care are using clear text. Individual record linkage can also be achieved using record linkage methods to protect privacy—for example, using “hashed” identifiers for linkage. In this method, a person’s specific attributes are replaced with a unique code that cannot be reversed to yield the original identifiers.

7.7.1 Geolocation Data Linkage

An alternate means to link data to a participant is through a home (i.e., residential) address or another location-based proxy. “Geocoding” of a participant to a specific geographic region enables inclusion of spatially dependent data, such as census, weather, or pollution data. We will build a geographic profile for participants who provide their residential and employment addresses through the PPI. All addresses will be prospectively geocoded into latitude/longitude coordinates. We will securely map addresses to geolocations through corresponding census tracts, block groups, and ZCTAs (ZIP code tabulation areas). Other data elements, such as percent urban/rural and population will be linked to participant geographic profiles.

A set of social, community, and environmental variables has been prioritized to populate an initial core linked dataset. This core set includes American Community Survey Census data, USDA (U.S. Department of Agriculture) Food Access Research Atlas, Environmental Protection Agency (EPA) outdoor air quality and air toxicity data, National Oceanic and Atmospheric Administration weather and climate data, and health care facilities information from the Area Health Resources File. Each of these datasets will be downloaded into the program’s secure environment (for their entire covered regions) and matched to each participant without sharing participant geolocations with these external entities. In time, more variables may be added to the core set as they are identified.

We will also investigate mapping in more complex environmental datasets from the EPA or other resources, such as daily air particulate matter readings, which are not constrained to standardized formats and have varying frequency of data collection. Many of these data elements may require complex modeling and curation and would be included based on investigators’ interest in such data. The DRC will facilitate the necessary linkages between the needs of investigators and the complex environmental data sources to generate relevant and interpretable datasets. Over time, these linkages may lead to methods or curation that will allow for complex environmental datasets to be considered “core” variables and thus available to all investigators.

7.7.2 Other Types of Data Linkage

Examples of data sources that may be valuable to link within the *All of Us* Research Program in the future include:

- Social Security Death Master File. The Social Security Administration generates a list of deceased people in the United States. Although in recent years updates to the

file have been delayed, linkage to this file can identify people whose death is not documented within an EHR.

- Pharmacy system data. Pharmacies, pharmacy benefit managers, and health information networks often contain medication prescription and dispensation data beyond any single institution's EHRs. Early conversations with SureScripts, a health information network provider, revealed that SureScripts is under a Business Associate Agreement with institutions holding the original data and would need additional approval from participants to share data for linkage with the program. SureScripts does use an internal Master Patient Index for purposes of linkage and can use this for linkage with the *All of Us* Research Program data. A Master Patient Index is a database that tracks all the possible identities for individuals within a system.
- When available, we would seek to include claims data. Private and public payers collect service and payment data on care received that may span multiple care sites. These data may lack some clinical details but often provide broader coverage of the providers, procedures, and costs associated with the care of the individual. Access to these data is often restricted and requires significant additional approvals and cost. Note that many insurers make some electronic claims data (e.g., Explanation of Benefits) available directly to patients, who can decide whether to share the data downstream.
- Health registry data. Most states and territories require mandatory reporting of cancer cases to a central, non-public registry administered by the CDC. These data cover 96% of the United States population and may provide more detailed data related to cancer cases (e.g., tumor type or stage) than found within the EHR. Additionally, many sites also maintain cardiothoracic, device, and other registries. When available, we would seek to include health registry data in data uploads from HPOs or through obtaining other national health registries derived from clinical data.

While the primary consent encompasses data linkage, it is anticipated that prior to linking participant data with external sources, an amendment will be filed with the IRB for any linkages to "health registries" or "claims data" that require the DRC to share participant-identifying information to an outside entity. Such submissions would detail the data to be linked and the general methods for doing so. No additional participant consent will be undertaken. The consent discusses that identifying information may be shared in this process.

7.8 Early and Long-Term Participant Involvement

7.8.1 Early Communication Workflow

A communication workflow sample is provided to give IRB members a snapshot or "wireframe" of the business logic and strategies to keep our *All of Us* participants actively involved as they complete stages of the data collection process (see Figure 7–2: Data Workflow Sample for Participants).

The Participant Portal will deliver a message to the participant following successful consent. The transactional notification message sent post-consent will define the purpose and content of the PPI module. The message will also welcome the participant to start the first PPI module. If the participant is inactive for a certain amount of time while working on

information that would be of interest to them, details on utilizing program data, and the scientific underpinnings of the program.

Program updates:

- Regular participant newsletters (bimonthly or quarterly that could include program milestones, new program features, enrollment numbers, events, or new findings.)
- Notifications, such as EHR reauthorization and security alerts.

A central tenet of long-term involvement is that the participant will control both the frequency and method of communication from the program. For example, the participant can choose not to be informed of some types or all types of new studies, or ask not to receive the newsletter. Participants will also be able to unsubscribe to all future communications except for required notifications (such as essential security alerts, if applicable). Those who select this option would no longer be contacted directly or invited for follow-up procedures. This option would allow continued use of information and samples already provided and would still authorize further collection of electronic health record information from their automated database linkage.

Program communications will primarily be conducted electronically (e.g., email, in app messaging). There will be a notification center (wall feed) in the Participant Portal for general messages and a banner on the home screen for high priority alerts (e.g., invitation to schedule the physical measurement and biospecimen collection visit). In the future, when individuals are able to register with a phone number instead of an email address, there will also be capabilities for SMS (short message service) communications. The need to develop paper and phone outreach processes for participants without email or mobile phones will be evaluated.

Participant-facing content not previously approved by the IRB will be submitted to the IRB separately. In the future, we plan to give participants the opportunity to share personal reasons for joining the program so that participants can learn more about why others have joined and what benefits they have experienced from the program.

8 Risks/Benefits Assessment

There may be risks, discomforts, and inconveniences associated with participation in research; these deserve careful scrutiny. The *All of Us* Research Program is not a medical treatment study. Joining the *All of Us* Research Program does not include activities associated with the risk of harm to participants nor adverse medical events, with a few exceptions.

8.1 Risks

8.1.1 Loss of Privacy/Confidentiality

The primary risks are the potential loss of a participant's privacy and the loss of confidentiality of a participant's personal health information. These risks will increase as a participant contributes more data to the *All of Us* Research Program. Over time the risk of re-identification becomes greater as there are more data sources to triangulate a participant's identity.

8.1.1.1 Privacy

All data collection—including administration of questionnaires—will be conducted in a private room or area in a location of the participant's own choosing, if they use the web or phone application. All participants, regardless of path of entry (HPO or DV), may choose to complete the consent modules and PPI in a private location of their choosing and are not required to complete these activities on site.

8.1.1.2 Confidentiality

All directly identifiable information will be protected by systems meeting or exceeding the Federal Information Systems Management Act (FISMA) Moderate standards and authorized to operate by NIH and the NIH Office of the Chief Information Officer (OCIO). The HPO-owned devices used to register and collect participant information will be shut down automatically after a few minutes of non-use. Transmission of information between sites also complies with high standards of security and is included under the review and approval purview of the NIH OCIO.

There is a risk that a third party may ask the *All of Us* Research Program to disclose information about a participant without their permission as part of legal or other claims. The NIH has issued Certificates of Confidentiality to all program awardees, including HPOs, DV sites, and vendors that cover activities related to the *All of Us* Research Program. Under these Certificates of Confidentiality, anyone using or in possession of copies of the data is prohibited from disclosing, except in specific circumstances, the names of research participants or any information, documents, or biospecimens that contain identifiable, sensitive information collected or used in the research program, including in response to a subpoena. The research program expects awardees and sub-awardees to protect participants' privacy and use all available legal measures to oppose such requests. However, if data are disclosed for any reason, that information is inadmissible in any legal, administrative, or other proceeding.

8.1.2 Physical Measurements

Participants may feel uncomfortable with some of the physical measurement procedures and/or results from those measurements. The weight and waist/hip circumference measurements themselves, plus others such as blood pressure and pulse, may lead to embarrassment or concern by participants. These procedures are standard medical procedures and pose no additional risk to participants other than their discomfort of potentially working with someone who is not their personal health care provider. To minimize these risks, all physical measurement procedures will be performed by trained program staff and will be carried out in the most respectful way possible. Participants will be reminded at the beginning of their physical measurements that they may opt out of some or all physical measurements without any impact on their ability to still participate in the program.

8.1.3 Participant-Provided Information (PPI)

Sensitive information may be revealed while completing the PPI and/or during the study. Completing the surveys or questionnaires may cause fatigue, frustration, anxiety, or boredom with the time it takes; participants will be reminded that they may take a break at any point. Completing the questionnaires may cause some people to feel emotional distress. All health survey questions will be optional; therefore, participants do not have to answer questions they choose not to answer.

8.1.4 Biospecimen Collection

Blood sampling risks include bruising of the arm and fainting. The modest amount of blood drawn, up to 50 mL, should not have any adverse physiological effects, nor should it lead to any long-term distress. Risks for blood-borne pathogens from accidental needle sticks and during sample processing exist. With venipuncture, approximately 5% of people may faint, feel nauseous, or feel dizzy; a bruise may also form at the puncture site. The risk of a blood clot forming in the vein is about 1 in 100, while the risk of infection or significant blood loss is 1 in 1,000. Trained program staff will use standard sanitary biological specimen collection safety protocols for collection and processing of samples (e.g., antiseptics, gloves, and appropriate clothing). All objects that come in contact with bodily fluids will be disposed of in appropriate biohazard waste containers.

8.1.5 Access to Electronic Health Records

Throughout the *All of Us* Research Program, trained program staff will access participant's EHR data. There is a risk of loss of confidentiality, as described above. This risk will be further minimized through robust standard operating procedures regarding EHR access and abstraction. In addition, program staff will complete the required training relevant to their activities, such as training regarding Human Subjects Ethics, the Health Insurance Portability and Accountability Act (HIPAA), Responsible Conduct of Research, and Good Clinical Practice as is appropriate for their role in the *All of Us* Research Program.

8.1.6 Participant Re-Contact

Participants will be re-contacted from time to time for follow-up. This may be annoying to participants over time; however, they will be reminded that their participation is voluntary, and they do not have to participate in any procedures. Participants can choose the frequency with which they are contacted, they can pause their communication from the program, and they can elect to withdraw participation.

8.1.7 Unknown Risks

Participants will be informed that the study may include risks that are currently unknown. When possible, the *All of Us* Research Program will inform the participant if new risks are identified that could affect their decision to participate.

8.1.8 Incidental Findings

The required physical measurements may uncover an abnormal value that may be actionable. See Section 10.4, Individual-Level Information Access Processes, for procedures for managing emergent and urgent medically actionable findings. Participants

may experience stress as a direct result of receiving health findings/measurements that may be indications of illness or be inconsistent with their understanding of their health status. Cost for emergency services and/or follow-up care associated with a value that is deemed to require attention will be the responsibility of participants. The *All of Us* Research Program does not assume responsibility for fees associated with responding to any emergent or urgent situations for medical care or transportation associated with existing conditions uncovered during the course of participation in the research.

8.2 Benefits

The *All of Us* Research Program has potential societal benefits as a robust research resource that can facilitate the exploration of biological, clinical, social, and environmental determinants of health and disease. The program aims to enroll one million or more participants across diverse populations from across the United States to provide insight into the substantial inter-individual differences in physiology, risk of disease, and response to therapy. The information and biospecimens collected will become a useful resource for researchers to investigate why some people develop certain health conditions while others do not. The *All of Us* Research Program invites participants to become partners in the data gathering and research process through various means, including through data return and as citizen scientists investigating the data. Citizen scientists are individuals interested in science and contributing to discovery. Participant involvement will occur at all levels of the *All of Us* Research Program, including oversight, design, implementation, and evaluation. The combination of a highly engaged participant population and rich biological, health, behavioral, and environmental data will provide a key resource for social, behavioral, and biological influences of health investigations capable of ushering in a new and more effective era of American health care.

We anticipate that the societal benefits stemming from the *All of Us* Research Program will accrue over time and will primarily advance future disease prevention and treatment strategies. There is no guarantee, expectation, or assertion that a participant will directly benefit. However, potential indirect benefits to participants in the *All of Us* Research Program include:

- **A chance to learn** about health indicators and access own data
- An opportunity to help develop new treatments and screening approaches to **fight disease** and improve the health of future generations
- An opportunity to **ensure that your community is included** in research studies that may lead to new understanding and new treatments
- The chance to **be part of a movement**, to make our healthcare more precise, more personal, and more effective
- Have the potential to be invited to participate in **future studies** involving *All of Us* participants

8.2.1 Access to Information

Participants will have access to their physical measurements and PPI responses via the Participant Portal being developed. As additional information types are collected, we will seek to provide access via the Participant Portal in the spirit of the program's value and in

the hope that by empowering participants with information and data they may improve their own health.

8.2.2 Screening Physical Measurements

Participants who undergo physical measurements will receive their personal data, along with information about the normal ranges. They will be told when their measurements are outside the norm. Participants may benefit from increased awareness of their health status and identify issues that warrant discussion with a health care provider (e.g., elevated blood pressure that, if confirmed, may warrant lifestyle modification or antihypertensive medication).

8.2.3 Opportunity to Participate in Ancillary Studies

Depending on their chosen communications preferences, eligible participants may be contacted about opportunities to participate in future research studies. They may also be invited to participate in clinical trials of targeted interventions and therapies.

8.3 **Risk/Benefit Analysis**

The goal of the *All of Us* Research Program is to create a public resource for scientific investigation and a research infrastructure that can be leveraged to improve human health. As noted above (Section 8.1, Risks), we acknowledge potential risks that may be incurred by study participants as well as strategies in place to minimize these risks. Although benefit to individual participants is not a specific aim of the *All of Us* Research Program, participants may nonetheless derive indirect benefits (Section 8.2, Benefits). Taken together with the scientific value of the program, the overall benefits outweigh the risks of participation.

9 **Issues to Consider**

The program will be conducted in accordance with the Belmont Report and OHRP [Common Rule](#).

9.1 **Payment for Participants**

9.1.1 Payment for Participation

Participants will be offered \$25 for their participation, following completion of the in-person physical measurements and biospecimen collection visit. Participants who need to complete these procedures in multiple visits may receive the \$25 upon the final visit. Provisions will be made for participants who are unable or unwilling to complete the full physical measures and biospecimen protocol while at the site. Payment decision will be recorded. In addition to the \$25 payment, participants may be eligible for transportation or parking costs, based on the site-specific business practices of their enrollment location. If the participant withdraws his/her participation, s/he will not be expected to return the \$25.

9.1.2 Intellectual Properties and Rights to Royalties

Data collected in the *All of Us* Research Program may be used to discover or create new products, or tests, and some of these may have commercial value. NIH, the program, scientists, or institutions that may benefit from these commercial products will not compensate participants whose data have been used to create these products or tests. The *All of Us* Research Program data will not be sold/distributed for commercial benefit or for marketing purposes. The CAPS will serve as the steward of the resource.

9.1.3 Compensation for Injury

No serious injuries are anticipated as a result of participating in the *All of Us* Research Program. However, if a participant is injured as a direct cause of their involvement in the *All of Us* Research Program:

- Trained program staff will assist the participant in obtaining immediate care if warranted by the injury.
- The *All of Us* Research Program HPO awardees or DV partners will pay for the cost of immediate medical care to treat the injury and take responsibility for answering any liability claims regarding the injury; institutions may bill the participant's insurance at their discretion.
- The participant's injury will be evaluated according to institution-specific protocol to determine whether the injury was a direct cause of participation in the program.
- If the research injury requires medical care beyond the immediate treatment, cost of follow-up care will be the responsibility of the participant and their insurance company; if the participant does not have insurance or if the insurance company will not pay, the participant will be responsible for these costs.
- Participants will not be otherwise compensated for their injuries.

9.2 **Handling On-Site Reportable Events**

The *All of Us* Research Program clinical partners will provide applicable accreditations and policies and procedures—and will ensure relevant training of all program staff—to assure appropriate processes are in place for responding to situations when physically working with the *All of Us* Research Program participants in their clinics or at their facilities. These policies and procedures will be collected by the NIH Program Officers and filed as part of Institution-Specific IRB Applications to this Operational Protocol. It will be important to ensure that clinical partner sites have procedures in place for responding to incidents such as:

- Physical injury that occurred while on site or during the act of the physical measurements and/or blood draw. For instance, known risks associated with specimen collection are:
 - *Blood draws*: The more common known risks of drawing blood include discomfort or pain, bruising, bleeding at the site, nausea, lightheadedness, and fainting.
 - *Saliva*: *No known foreseeable risk in the collection of saliva*
 - *Urine*: *No known foreseeable risk in the collection of urine*
- Verbal and nonverbal indications that the individual may be a victim of physical and/or emotional abuse

- Indications of suicidal thoughts
- Misconduct on the part of the participant that negatively affects the center/clinic or its patrons

Unexpected adverse events and unanticipated problems which are not consistent with the known or foreseeable risks of adverse events associated with the research procedure or the expected natural progression of any underlying disease, disorder, or condition of the person experiencing the adverse event will be documented by sites PIs. These reportable events will be filed with NIH and the IRB in accordance with HHS requirements for disclosing reportable events and unanticipated problems.

9.3 Participation options: Un-enroll and Withdrawal Procedures

Participants may, at any time, stop their participation from the *All of Us* Research Program without giving a reason and without penalty. They may do this on their own by editing their participant status on the Participant Portal or by contacting the Support Center, who will guide them to withdraw through the Participant Portal. In addition, investigators may withdraw a participant, if necessary and for any reason, including ineligibility arising during the program or retrospectively if overlooked at enrollment or inappropriate actions directed toward AoURP staff.

Participants will receive an email and/or letter to confirm recording of their updated participation status. They will also be informed that it may take up to two business days to propagate changes to their participation status throughout the AoURP system. A summary of participation options AoURP plans to implement is presented below (Table 9–1: Participation Options) followed by details for each option.

Participants are informed during the consenting process that the program will maintain their name and basic contact information for regulatory requirements and quality control (e.g., as part of archived consent forms). Similarly, all the records contained in the *All of Us* Biobank laboratory information system must be maintained. However, such information will not be shared with researchers accessing the AoURP resource. Participants are also informed that data and specimens already used in research cannot be recalled nor destroyed. For instance, it is not possible to destroy all sample remnants and information already distributed or analyzed.

An abbreviated version of the participant's record will be maintained on HealthPro with limited data, such as participant ID, first name, last name, date of birth, date of consent, and date of un-enrollment or withdrawal. Other data will be removed from the HealthPro record. The purpose of maintaining this subset of data in HealthPro is to have an accurate record of participation status for site staff to consult. Staff can thus take care to not proactively approach or otherwise contact via any modality (phone, email, or text) un-enrolled or withdrawn participants and can maintain records of all participants to whom \$25 was distributed.

Table 9–1: Participation Options

	Un-enroll	Withdraw	Deceased
Data collection	No	No	No
User Access to their Participant Portal Account	Yes	Yes	No
User Contribution to their Participant Portal Account	No	No	No
Researcher access to data and samples for new research studies	Yes	No	Yes
Messages from AoURP	Yes	No	No
Reactivation	Yes	Yes	No

9.3.1 Un-enroll

Participants will be able to un-enroll (or “pause” participation) if they wish to suspend active participation but authorize continued use of their existing data and biospecimen for future research (i.e. feature in preparation). No new data will be collected either actively or passively (i.e. through data linkage or personal health technology) after the effective date of un-enrollment. The participant’s record on HealthPro will be flagged to indicate that the participant no longer wants to be contacted about follow-up opportunities.

Ideally, un-enrolled individuals will be able to keep their account on the Participant Portal. However, their account will be frozen so that participants cannot submit any new data.

Re-enrollment in the program is allowed but requires re-consent. Any new data collected will be linked and appended to a participant’s original dataset if they re-enroll using the same name and email address.

9.3.2 Withdrawal

The withdrawal option is for participants who wish to leave the program and do not want their data and biospecimens to be available for future research. Withdrawal status will be documented in the program database with a copy of the consenting document for proper regulatory compliance. No new data or samples will be collected, and the participant will not be contacted about follow-up program opportunities. Data from withdrawn participants already contained in existing versions of the research database will remain available to promote reproducibility but will be removed from future versions of the research database. Stored biospecimens that have not been analyzed or distributed to qualified researchers will be destroyed.

As for un-enrolled individuals, participants who withdraw will be able to keep their account on the Participant Portal. However, their account will be frozen. No new information, data, or results will be added (feature in development).

If a participant wishes to re-join the *All of Us* Research Program at a later date, they may do so. However, they will need to create a new participant account, re-consent, answer the PPI surveys, and donate new biospecimens. Their new data will not be appended to their

prior account, even if they use the same name and email address. They will not be eligible to receive \$25 for their return participation following completion of the new in-person physical measurements and biospecimen collection. Although this is stated in the consent form, the program may re-visit the decision.

9.3.3 Withdrawal After Death

As a default, existing data and biospecimens from deceased individuals will continue to be available for future research.

However, AoURP is considering giving participants the choice to indicate their preference to be withdrawn from the program after their death. Participants who select this option would have all links between their identifying information and their research data broken and their specimens destroyed from the Biobank upon confirmation of their death. Our planned process includes confirmation of death through an annual query of a national death index with the participant's identifying information (including social security number) for those participants who have provided it. However, this process may not be sufficiently timely or accurate to ensure participant directives are followed. Participants would be informed in the process of selecting this option that automated linkages to death indices are imperfect, and about the importance of receiving a death certificate. The participant's family could contact AoURP with a death certificate to initiate withdrawal from the program. Family requests would be honored exclusively for participants who had selected this option. At the point of receiving a death certificate or affirmative linkage via a death index, AoURP would follow the same procedures as a standard withdrawal.

9.4 **Destruction of Specimens**

Because blood samples could potentially contain biohazardous materials, the central program laboratory (i.e., Mayo Medical Laboratories) will not be able to return unused specimens back to participants or their families. In the event that samples collected do not meet the criteria to be sent to the central laboratory, sites will follow their institutional policies for sample destruction.

In an effort to respect participants' values and beliefs, AoURP will enable a cultural ceremony performed by an accredited tribal healer or medicine man to administer blessing or last rites to samples prior to their destruction. It is estimated that such cultural ceremonies will take place twice a year at the central laboratory. Samples tagged for destruction under this option will be stored until the ceremony takes place.

Additional site-specific processes for culturally sensitive practices may be developed and approved through Institution-Specific IRB Applications.

The central laboratory will dispose of biological specimens in accordance with [Occupational Safety and Health Administration](#) (OSHA) medical waste disposal guidelines.

10 Access to Individual-Level Information for Participants

10.1 Principles of Individual-Level Information Availability

The *All of Us* Research Program information access procedures, including access to data and results, will adhere to principles outlined by the White House’s [*Precision Medicine Initiative: Privacy and Trust Principles*](#) and [*Data Security Policy Principles and Framework*](#), including transparency, timeliness, and participant empowerment.

- Uncertainty of meaning or concern about impact on participants should not be a reason for the *All of Us* Research Program to withhold information from participants.
- Where possible, information must be presented in a culturally appropriate and language-specific manner.
- The default bias for information access must always be to make the information available to participants as soon as possible.
- The choice to access and review information will be at the discretion of the participant; when possible, participants must be able to set preferences for the type, method, and frequency of information they may receive and will be allowed to change these preferences at any time.

As individual-level information becomes accessible, it needs to be readily and easily available to participants in an array of data-specific and results-specific formats and interfaces that may include:

Data-specific formats and interfaces:

- Hard copy of the physical measurements. A template form will be used to give participants their physical measurements.
- Machine-readable/structured data available for direct download and through application program interfaces (APIs).

Results-specific formats and interfaces:

- Visual/interface-based tools and interactive dashboards. Participants can view results through their program account on the secure Participant Portal.
- Multiple information-sharing platforms and interfaces will be created to provide flexibility for access to individual level results (e.g., infographics, web-based dashboard, mobile apps, newsletter, email, mail). These platforms may also be used to return group- and program-level results.

We anticipate that participants’ access to their own information—including their experience throughout that process—is a critical component for maintaining their long-term engagement with the program.

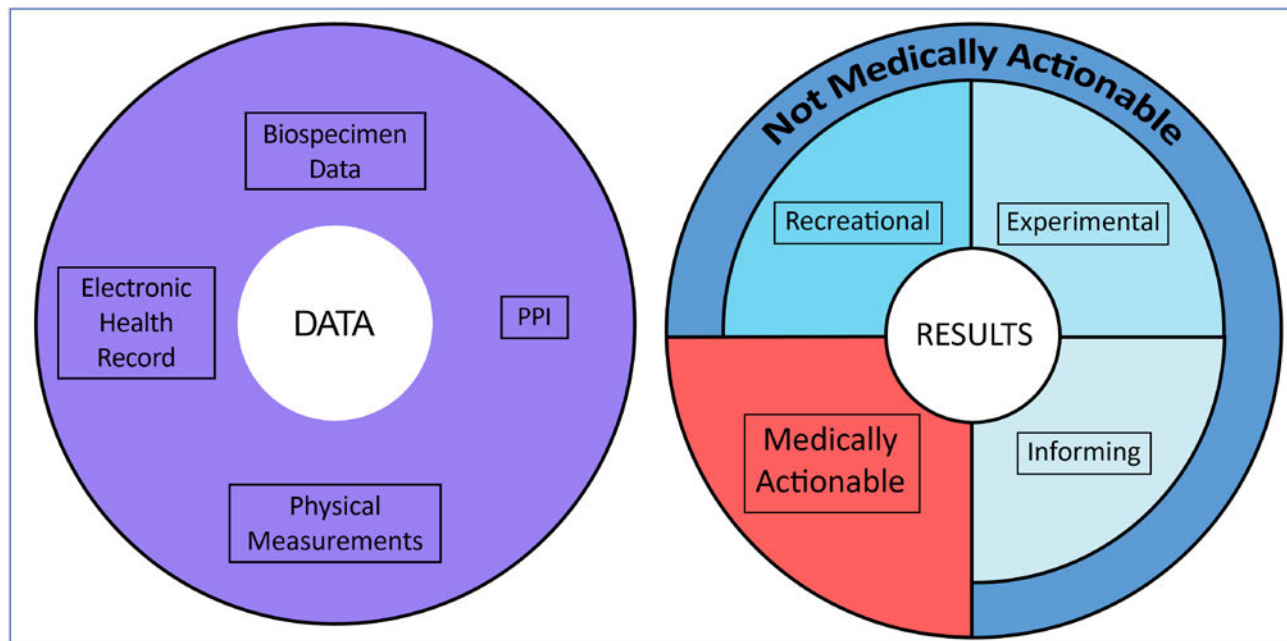
10.2 Individual-Level Program Information

The *All of Us* Research Program will gather and generate a tremendous amount of information about each participant as an individual. Individual-level program information falls into two categories: data and results.

Individual-level data includes all information that participants contribute (e.g., PPI, physical measurement data, EHR data) as well as data that is generated from biospecimens (e.g., genetic sequence data from a participant’s sample) (Section 10.2.1, *All of Us* Research Program Individual-Level Data). Consistent with the core principles of the program, participants will have access to the individual-level data they contribute.

The second category of individual-level program information is results. Individual-level results are the interpretation of specific participant data. These results fall into two main categories: medically actionable and not medically actionable.

Figure 10–1: *All of Us* Research Program Individual-Level Information: Data and Results



10.2.1 *All of Us* Research Program Individual-Level Data

Consistent with the core values of the *All of Us* Research Program, participants will have access to all their contributed program data and individual results. Participants may contribute:

- PPI responses
- Physical measurements
- Electronic health records and Part 2 records
- Biospecimens
- Other types of data in the future, such as sensor measurements

Data derived from these contributions, such as genetic sequencing data and wearable sensor data, are considered individual-level data. In addition to instances of aggregate-level readouts of the individual-level data, data will be available to participants without interpretation except where explicitly stated otherwise by AoURP. Participants are empowered to decide if and when to access their individual-level data. They will not have to receive such information but will have the option to do so. The exception to this would be data derived from studies whose data is not necessarily resolvable at an individual level or is not considered a test with high validity.

10.2.2 *All of Us* Research Program Individual-Level Results

Medically actionable results are results that could be used to inform the medical care that participants seek or receive to maintain their personal health. Participants may need to

complete a supplemental consent process or some other informing interaction prior to unlocking their medically actionable results. An example is an emergent blood pressure measurement.

Not medically actionable results are results that could inform participants' decision making but not directly inform the medical care that participants seek or receive to maintain their personal health. Examples of not medically actionable results are:

- Measurements within an expected range (i.e., "normal" cholesterol)
- Recreational results, such as taste aversion
- Experimental results from novel assays

It is important to note that not all participants will choose to receive their individual-level results. Participants will be free to share their results with anyone they choose. The rationale for not contacting the participants' health care providers directly include:

1. Not all participants will have a health care provider
2. This is not health care, or a clinical trial; it is an observational study.
3. All participants should be treated with the same standardized protocol; participants should have the freedom to make the decision of if, when, and how to communicate individual-level results information to their health care provider

To facilitate understanding and sharing their results, we will develop easy-to-read templates.

10.2.3 Return of Results: Framework

The *All of Us* Research Program is beginning to develop a framework and set of processes for returning results to participants. This framework will:

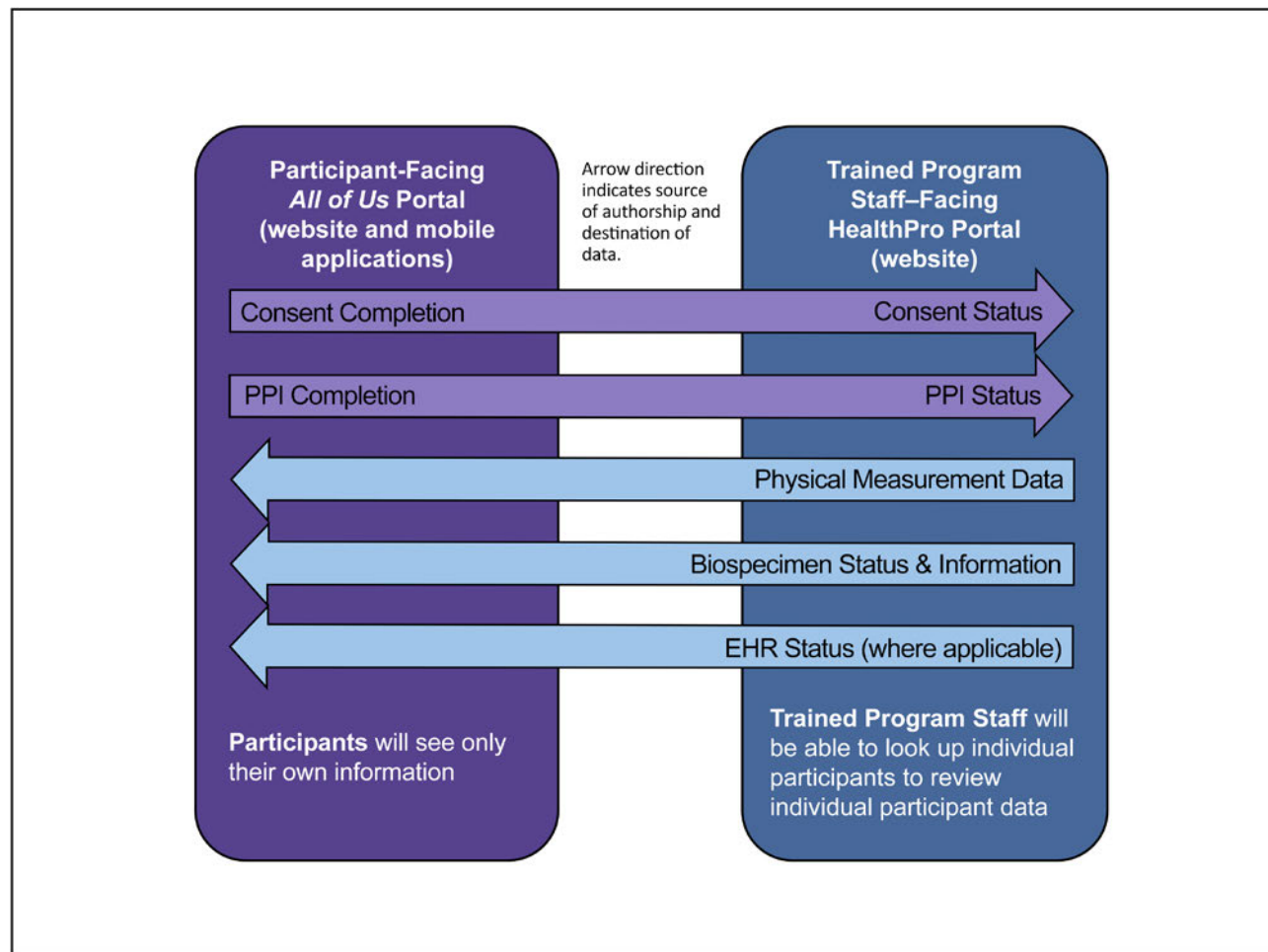
- Lay out the principles for returning *All of Us* Research Program data and results to participants
- Establish guidelines for applying the framework to existing and new data as well as result types
- Develop data and results type-specific access and return policies (which will grow over time), allowing for a participant's individual preferences of the types of data they would like to see or have actively returned to them.

10.3 Information Access Technologies

10.3.1 All of Us Research Program Participant Portal

The core public-facing program enrollment and communication tool is the program's Participant Portal. In addition to providing program updates and messages to participants as described above, participants will be able to access their individual-level information on their personal account using this portal (feature in development). Participants will have access to their responses to PPI questionnaires, the values from their physical measurements, their responses to snap surveys, notifications that they have provided EHR data, and potentially information about the wearables they've chosen to integrate.

Figure 10–2: Data Flow for Participants and HPO Staff



Access to certain data types, such as genomics, will be a multi-step process. For instance, participants will need to first consider the pros and cons of obtaining their genomic information and unambiguously consent to unlocking access to these data through the Participant Portal. Genetic counselors may be called upon to explain certain genomics results to the participants when their genomics data is first unlocked; planning for how to provide this service at scale is currently underway in the AoURP Omics Committee and will be presented at a later time to the IRB.

The Participant Portal User Interface is being updated. It will integrate the IRB-approved materials such as the enrollment and consent process, site-pairing and visit scheduling, PPI, measurements, and notifications. Screenshots of the Participant Portal illustrating the user experience will be submitted to the IRB as a protocol supplement. A future portal version will include a dashboard where participants can view some of their data compared to the aggregated data generated through the *All of Us* Research Program. Furthermore, the DRC will maintain the Research Portal to enable access to the program data, including a public portal where participants will be able to view aggregate data and a registered access portal where participants, as citizen scientists, will be able to access data with personal identifiers removed.

10.4 Individual-Level Information Access Processes

10.4.1 Physical Measurements—Access to Information

In the spirit of the *All of Us* Research Program values (Section 2.1, What Is the *All of Us* Research Program?), all physiologic and anthropometric measurements logged through the physical measurement process will be stored in the “Participant Record” through the PTSC application (web and mobile) and will be accessible by the participant through the Participant Portal (feature in development). The physical measurements data may also be given to participants in hard copies provided by trained program staff at the time of the physical measurement visit. A template form (hard copy) will be used to give participants their physical measurements in a consistent manner.

As described above (Section 7.3, Physical Measurements), the physical measurements will include physiologic (e.g., blood pressure, heart rate) as well as anthropometric (e.g., height, weight, waist and hip circumferences) measurements. Body mass index will be calculated automatically from measured height and weight.

Participants will also receive the aggregate-level measurement values from publicly available information until there is a critical mass to provide an equivalent comparison using program data.

Another goal of the *All of Us* Research Program is to couple the information with educational materials to promote understanding. These educational assets may include:

- Normative values and evidence-based guidelines for components of the physical measurements specifically focused on the individual’s demographics, such as sex, age, and race
- Links to websites (e.g., WebMD, PatientsLikeMe) that provide information pertaining to each measurement
- Educational videos, produced by the *All of Us* Research Program (to be developed), that provide background information on the various components of the physical measurements collected through the program

The *All of Us* Research Program is an observational study, and therefore none of the information provided constitutes clinical recommendations. Information returned to participants, including those considered medically actionable, would need to be confirmed independently. As we develop modules to return information, we will develop unambiguous language to remind participants that the *All of Us* Research Program is an observational study and is not designed to diagnose or treat any medical condition or serve as a substitute for regular medical care. Modalities for participant information access will provide a disclaimer that the participant may wish to consult a health care provider to follow up on physical measurement information, and any questions the participant has about the impact of program-related information on their personal health or clinical management should be directed to their health care provider. If a participant does not have a regular provider, the trained *All of Us* Research Program staff will provide referrals at participant request to appropriate organizations that work with underserved populations in their region.

As the public-facing and individual participant information dashboards are developed, they will be presented as an amendment to the Operational Protocol, to provide the IRB with the opportunity to provide guidance.

10.5 Physical Measurements—Return of Medically Actionable Results

Although the physical measurement component of the *All of Us* Research Program does not constitute clinical care, we anticipate that a small but important percentage of individuals will have medically actionable results that, if left unaddressed, might have adverse consequences for the participants' health.

Clinically actionable findings from the physical measurements are limited to blood pressure and heart rate, as defined below (Table 10–1: Medically Actionable Findings at the Time of Baseline Physical Measurements). Trained program staff will record physical measurements via HealthPro. If a measurement falls outside the range considered “normal” per the *All of Us* Research Program protocol, a message will pop up on the HealthPro screen. After confirming the measurements, the trained program staff will ask the participant whether these measurements are typical. A script was developed to guide discussion about measurement findings with the participant and to draw attention to certain measurements.

Participants requiring immediate and expedited referrals will be managed per institution-specific policies and procedures, as declared in the Institutional-Specific IRB Application. Similarly, if, in the opinion of the trained program staff performing the physical measurements, the participant appears to be clinically unstable for any reason, site-specific policies and procedures will be followed.

Emergent and urgent actionable findings will not be sent to a provider. Instead, a “Physical Measurement” document or card will be provided to the participant with their physical measurements, along with any urgent or emergent findings specifically called out. The participant can use this card to follow up with a provider of choice. Trained program staff will use the script above to call the participant's attention to any emergent or urgent actionable findings listed on the card.

Table 10–1: Medically Actionable Findings at the Time of Baseline Physical Measurements

	Emergent	Urgent
Systolic Blood Pressure*	<ul style="list-style-type: none"> • >200 mmHg • <100 mmHg and any symptoms of hemodynamic instability*** 	<ul style="list-style-type: none"> • 180–200 mmHg
Diastolic Blood Pressure*	<ul style="list-style-type: none"> • >120 mmHg • <60 mmHg and any symptoms of hemodynamic instability*** 	<ul style="list-style-type: none"> • 110–120 mmHg
Heart Rate**	<ul style="list-style-type: none"> • <60 or >100, not known to be usual for the participant, and any symptoms of hemodynamic instability*** • <60 or >100 and hypotension (systolic blood pressure of <90 mmHg) without symptoms of hemodynamic instability*** 	<ul style="list-style-type: none"> • Asymptomatic heart rate <50 beats per minute or >120 beats per minute, not known to be usual for the participant • Heart rate >100 beats per minute and irregular • Pulse unable to be determined via digital cuff (following verification by manual pulse determination when possible) unless confirmed by participant that an irregular heart rhythm is already a known condition
Minimum Site Response	Participant is immediately advised of the need of emergent care, and if agreed to by participant, trained program staff will refer the participant to emergency care (e.g., site-specific emergency room or 911); refusal will be documented according to site-specific policies and procedures	Participant is immediately advised to seek medical attention and to notify their provider, or trained program staff may offer to help locate an urgent care facility and coordinate transportation to the facility as needed


* Based on Eighth Joint National Committee (JNC 8) recommended blood pressure goals. [Abel et al. 2017-
doi:10.4103/1947-2714.168669]

** Based on the American Heart Association recommended target heart rates.

***Hemodynamic instability is defined by, and will be prompted within HealthPro at the time of data entry meeting numeric criteria, to include (1) changes in mental status (reduced alertness and awareness, confusion, possible loss of consciousness), (2) chest pain, (3) shortness of breath and/or rapid breathing, and/or (4) cold, clammy skin.

HPOs/DV sites can access the template for the “Physical Measurement” card via the Wondros *All of Us* Asset Portal. The card is also included in the biospecimen kit for the DV sites.

Figure 10–3 Example of Physical Measurement Card—Co-Branded



Place Partner Logo Here

Thank you for taking part in the *All of Us* Research Program.
By sharing your information, you're helping shape the future of health care.
This form has your physical measurements from your visit today.

Date of Visit: _____

Blood Pressure (Systolic/Diastolic): _____ / _____ **Heart Rate Beats Per Minute (BPM):** _____

Height: _____ **Weight:** _____

Body Mass Index (BMI): _____




Waist Circumference: _____

Hip Circumference: _____

You will see blood pressure, heart rate and BMI information on the right. This is to give you a broad sense of what is thought to be "normal" for an average person. Your "normal" may be different from this for many reasons. These reasons may include your age, level of fitness, and general health. Concerns or questions about your measurements? Please speak to your health care provider or contact the *All of Us* Support Center at 1 (844) 842-2855 or help@joinallofus.org.


The National Institutes of Health offers many resources to help people learn more about heart health. It also has tools to help people maintain a healthy weight.

Visit: <https://www.nhlbi.nih.gov/health>.

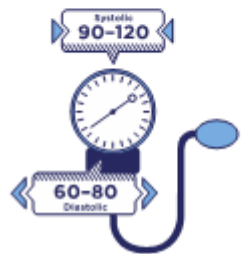
☐ Your findings suggest a potential concern with your blood pressure or heart rate. We recommend an evaluation by a health care provider as soon as possible.

Adult Body Mass Index (BMI) Groupings:




(These apply to both men and women.)

Normal Blood Pressure Range:



Normal Heart Rate Range:



Precision Medicine Initiative, PMI, All of Us, the All of Us logo, and "The Future of Health Begins with You" are service marks of the U.S. Department of Health and Human Services.

joinallofus.org

Figure 10–4 Example of Physical Measurement Card—5 x7 format



Thank you for taking part in the *All of Us* Research Program. By sharing your information, you're helping shape the future of health care. This form has your physical measurements from your visit today.

Date of Visit: _____

.....

Blood Pressure (Systolic/Diastolic): ____ / ____

Heart Rate Beats Per Minute (BPM): _____

Height: _____ **Weight:** _____

Body Mass Index (BMI): _____

Waist Circumference: _____

Hip Circumference: _____

☐ Your findings suggest a potential concern with your blood pressure or heart rate. We recommend an evaluation by a health care provider as soon as possible.

.....

joinallofus.org

You will see blood pressure, heart rate and BMI information on the right. This is to give you a broad sense of what is thought to be “normal” for an average person. Your “normal” may be different from this for many reasons. These reasons may include your age, level of fitness, and general health. Concerns or questions about your measurements? Please speak to your health care provider or contact the *All of Us* Support Center at 1 (844) 842-2855 or help@joinallofus.org.

The National Institutes of Health offers many resources to help people learn more about heart health. It also has tools to help people maintain a healthy weight.

Visit: <https://www.nhlbi.nih.gov/health>.

Precision Medicine Initiative, PMI, *All of Us*, the *All of Us* logo, and “The Future of Health Begins with You” are service marks of the U.S. Department of Health and Human Services.



Normal Blood Pressure Range:



Normal Heart Rate Range:



10.6 Participant-Provided Information and EHR

Participants will provide various types of information to the program through questionnaires and other modules, which may include demographics, disease state, health information, lifestyle, data type, and/or location. A future version of the Participant Portal will include a dashboard where participants will be presented with a comparison of how their information lines up with aggregate-level information from the *All of Us* Research Program.

EHRs from DV participants will be integrated into the platform at a future date; see Section 7.6, Electronic Health Records (EHRs).

10.7 Access to Biospecimen-Derived Information (Non-Genetic)

10.7.1 Biospecimen Collection—Access to Information

In the spirit of the *All of Us* Research Program values (Section 2.1, What Is the *All of Us* Research Program?), information derived from a participant's biospecimen by the program will be made accessible to the participant in an appropriate, IRB-approved manner.

Participants will be able to access their biospecimen-derived information upon request. There will be information about the status of the biospecimen and information pertaining to biospecimen-derived data (if applicable), as described below.

10.7.2 Information on Biospecimen Status

Participants who opt to keep informed about their biospecimen status via the secure Participant Portal may receive the following (feature in preparation):

- A message thanking them for their donation
- Notification that their biospecimen has been received by the Biobank (e.g., "Congratulations, your specimen is in the Biobank")
- Educational information pertaining to the "journey" that their biospecimen donation will take (e.g., from a collection center to the Biobank, where the specimen has personal identifiers removed and sent to a research database)

10.7.3 Biospecimen-Derived Data—Notice of Future Addenda to Operational Protocol

Due to the wide number of assays that may be performed on biospecimens over the course of the program, it is impossible to adequately account for all potential types of information that may be generated, including "normal" and "abnormal" range findings and potentially clinically actionable information. Therefore, the program will implement a process whereby, as a specific assay is being planned, an information access plan will be developed in tandem and submitted to the IRB for review prior to initiation of that assay. Note that the AoURP will not allow HIV assay or testing of any type without the express written consent of participants, consistent with the law(s) of their state of residence. This approach does not prohibit the study of HIV status, as participants could self-enter their HIV status through future PPI modules or have it indicated via their EHR record or other linked data.

10.8 Access to Genomic results

Many participants will consent and contribute to the research program without being invited to provide biospecimens. For the subset of participants who are invited and elect to contribute biospecimens, DNA will be isolated and genomic analysis conducted. Participants will decide whether or not to receive the results. A separate return of genomic results consent process, policies, and procedures will be submitted to the IRB at a later date and will govern the return of results from select assays (Section 6.5, Electronic Consent).

11 Creation of the *All of Us* Research Program Resource

A primary end product of the *All of Us* Research Program is a curated dataset that will be made available through a Research Portal to support scientific investigation. The DRC is responsible for aggregating, managing, and curating the data that is made accessible through the Research Portal. Multiple streams of data will flow into the DRC, including PPI, data from physical measurements, biospecimen measurements, EHR data, data obtained through linkage with distinct external datasets (e.g., the Social Security Death Index) as outlined in Section 7.7, Data Linkage, and data from custom-built digital health technologies. The DRC collects these data streams into a **Raw Data Repository** (RDR). New individual-level datasets get merged with existing data from the same participants in the participant's study record, direct identifiers are removed from structured and unstructured data streams, and the data gets organized and curated into a **Curated Data Repository** (CDR). This transformation approach will include validation and implementation of phenotyping algorithms that extract variables of interest (e.g., diagnosis of coronary artery disease). The CDR is accessible through the Research Portal according to the AoURP Data Access framework. All data are encrypted at rest and during transfer, either from the source or to Consortium partners.

11.1 The Raw Data Repository

The RDR functions as a flexible, "append only" data repository capable of storing a variety of data in its originally received format. The primary role of the RDR is to act as the main data repository for the program and the final "source of truth." The secondary role of the RDR is to facilitate the consistent and secure transfer of data to and from external systems, including the PTSC, *All of Us* HPOs, DV partners, the Biobank, and approved external digital health technologies. The RDR contains many disparate sets of AoURP participant data, including identifiers like the participant's name and contact information. Data are never destroyed from the RDR, including after participant withdrawal, for regulatory and quality assurance purposes. The RDR is not accessible to anyone outside of a very limited number of RDR-authorized *All of Us* staff.

11.2 The Curated Data Repository

The curated dataset is the subset of the raw data that has been curated into tiers to enable its sharing with researchers and the public. The tier system accommodates sharing data under more or less stringent conditions to protect the privacy of individuals from whom the data is derived. New CDR datasets are periodically generated from the RDR. As part of this process, personally identifiable information (PII) is removed from participant data as

follows: PII from structured fields (e.g., Yes/No questions, selecting a birthdate, rating an experience from 1 to 10) will be replaced with code. Data from unstructured fields (e.g., doctor's notes, responses to open-ended questions) will be scrubbed with natural language processing, but 100% removal of PII from these fields cannot be guaranteed. For this reason, access to this free-text data will be highly controlled.

The CDR dataset remains on a distributed cloud-based data platform enabling authorized researchers to deploy computing resources and run analysis without moving the data to a new location. The end-to-end security and privacy measures of the cloud infrastructure support the confidentiality and integrity of the data. Researchers will be able to query the CDR data and execute their analysis code using the cloud infrastructure in the DRC's Research Portal.

Advantages of this approach include:

1. Security: Significant centralized resources can be brought to bear to secure copies of the data, and access can be more easily monitored and tracked by removing data "handoffs"
2. Cost: This approach avoids the need to store multiple copies of the massive dataset
3. Accessibility: Few groups have the infrastructure needed to support data on this scale, limiting its utilization
4. Elasticity: We can provide a pool of compute resources for needs that vary over time

11.3 The PTSC Data Repository

The PTSC also collects and retains copies of participant's data, including data from the Participant Portal, AoURP custom-built digital health technologies, and S4S-enabled EHRs (or other technology-enabled EHRs where applicable). In addition, it collects standard log information and digital usage data (e.g., how individuals use the Participant Portal, pages accessed, amount of time per page, overall navigation).

Data is stored at the PTSC for several reasons:

1. To support a user-friendly experience with the Participant Portal
2. To support quality improvement testing
3. To enable quality assurance testing

All data are encrypted at rest and during transfer either from the source or to the DRC. Personally identifiable information like first name, last name, date of birth and/or address collected during consent and account creation is encrypted along with all the other data on the PTSC database.

12 Post-Enrollment Engagement Strategy

The mission of the *All of Us* Research Program is "to enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care." Meaningful post-enrollment engagement with and retention of participants is critical to fulfilling this promise.

For the purposes of the program, “engagement” is used as an overarching inclusive term to describe the broad range of interactions between the program, people, and awardees and other organizations. Engagement includes information sharing, consultation, involvement and collaboration in decision-making, and empowered action in informal groups or through formal partnerships. Consistent with the program’s values, the engagement strategy is focused on empowering individuals and communities through greater access to information and data. This participant-focused engagement strategy may also improve the quality and quantity of data contributed to the *All of Us* Research Program.

Specifically, post-enrollment engagement differs from outreach for recruitment in that engagement provides the opportunity to interact with partners, where the outcome may be a bidirectional increase of general knowledge and increased partner input.

“Retention” describes efforts to encourage and support ongoing contribution to the program by participants. “Contribution” includes a broad set of actions to improve the amount and quality of data in the repository—from the donation of additional participant-provided information and reflection on and refinement of participant records by participants themselves, to the sharing of experiential feedback for the improvement of the program. Effective retention will improve the quality and quantity of data provided by participants and as such will improve the value of the *All of Us* Research Resource for all scientific uses. Retention will also benefit engagement efforts in that the repository may then be a more meaningful resource for participants as individuals and at the community and national levels.

Given the unprecedented scope and scale of AoURP, we recognize that there is currently no proven, effective long-term engagement or retention strategy for this type of very large longitudinal cohort program. Whenever possible, all strategic initiatives on engagement and retention will be designed as learning programs to enable effectiveness testing and will be informed by existing research efforts in community-engaged research.

12.1 Conceptual Framework

Framework discussions about engagement and retention often begin with examinations of motivation: Is someone extrinsically or intrinsically motivated to participate? Extrinsic motivations often take the form of direct payment but can also be longer-term “games” in which people accrue tokens such as points, badges, or “swag” in return for continued participation. Intrinsic motivations are often described via conceptual frames, such as relatedness, autonomy, proficiency, or purpose.

Within the Community Engagement Studios performed at Vanderbilt to inform development of the project, participants did not hesitate to ask for extrinsic “incentives” to encourage their participation. Many of the populations interviewed for these community engagement studios have traditionally been underrepresented in research and/or have histories of negative experiences with medicine/research (with little to no intrinsic or extrinsic benefit). They also often face greater barriers to participation, such as time and transportation. Extrinsic incentives are part of a sign of respect to these communities for their participation.

Intrinsic motivations are generally found to last longer, increase engagement, and increase adherence compared to extrinsic motivations (Boundless, 2016). Extrinsic incentives are known to improve retention rates (Booker et al, 2011; Brueton et al, 2014) but they are also commonly used for blood donors (which many cite as an example of altruism) (Costa-Font et al, 2013; Farrugia et al, 2010; Glynn et al, 2003).

The balance between intrinsic and extrinsic motivating forces in human subjects research leans away from extrinsic motivators and skews heavily to intrinsic motivation as a way of avoiding the hazards of undue influence and involuntary participation. By contrast, modern digital apps are designed for “stickiness”—the ability of an app to repeatedly bring its audience back into the app.

In our complete engagement and retention plan, we will list the various approaches, with notations on where there are complex interactions between them, as well as mitigation strategies where appropriate. Working from this conceptual framework allows us to specifically examine outreach efforts to ensure the program is motivating but not coercive—honoring the principle of informed consent in human research.

12.2 Approach to Engagement

The *All of Us* Research Program explicitly values participants as partners in research. We strive toward that partnership by creating an engagement strategy with participant partnership built intentionally into its structure. Engagement in the program will be a systematic, considered process, with the express purpose of working with groups of people—whether they are connected by geographic location, special interest, health condition, affiliation, or identification with issues affecting their well-being. The overarching goal of our engagement strategy is to create a program reflecting the needs, preferences, and priorities inclusive of the range of age, social, racial, ethnic, cultural, geographical, and health statuses of individuals across the program. Participants and their advocates will be involved in all aspects of the program, including governance, oversight, design, conduct, dissemination, and evaluation. We aspire toward maximum inclusiveness to ensure that all communities are respected and represented.

The word “community” is broadly intended to define groups of people such as participants, stakeholders, special interest groups, and citizen groups. Communities for the program may develop due to shared circumstances or interests of any kind—for example, geographic location, racial/ethnic identity, cultural group, shared beliefs, or experience with or interest in particular health conditions.

The engagement strategy will be designed to encourage multidirectional communication and participation in the program by individuals – those participating, their advocates, and interested community members – and organizations. As such, engagement strategies will be threaded through awareness, recruitment, enrollment, and retention activities. Key elements of the strategy include but are not limited to the following:

- Regular reminders to sites’ Principal Investigators and point-of-contact people of the program’s core values
- Verification of budget allocation to support impactful and inclusive engagement and retention strategies at all stages of the program

- Having 1 or 2 key personnel who are knowledgeable, culturally competent, sensitive, and personally accountable for the successful implementation of the engagement efforts
- Working collaboratively with engagement experts and sharing information and best practices
- Promoting a Community Emotional Quotient Approach (EQ) that resonates with the population served—i.e., designing an engagement approach that incorporates key elements attuned to and responsive to the needs of the community
- Designating key engagement voices as representatives on participant-facing committees, task forces, and work groups

We present some example engagement activities that will be undertaken at launch but that do not represent the complete or final engagement plan, outlining some initial tools and methods. We will submit a more developed engagement plan, including assessment metrics, to the IRB.

12.2.1 Examples of Interpersonal Engagement Activities

At the interpersonal level, we will leverage existing community health infrastructure to support meaningful engagement. For example, the New York Regional Medical Center (RMC) will use its “Each One Teach One” programming, where health topics are identified by a steering committee of community members; health information is then delivered back to the community via person-to-person conversation and through the web by medical experts. The Pittsburgh RMC created the multimedia Pitt+Me engagement platform to provide information about research generally and raise awareness of specific studies that may be of interest to community members. Overall, these regional initiatives promote personal positive experiences with study participation, fostering empowerment at the interpersonal level.

12.2.2 Examples of Community-Level Engagement Activities

Awardees will leverage local health centers and community gathering places (e.g., local pharmacies, blood banks, churches), including the specifically designed Mobile Engagement Asset (MEA) described previously, to engage participants at the community level. For example, New York’s “Come meet *All of Us*” will be its first engagement event and will include both an introduction to the *All of Us* Research Program and an opportunity for community members, scientists, providers, practitioners, and partners to meet and interact with the team who are bringing the program forward in the community. Pitt’s partnership with the Urban League of Greater Pittsburgh and more than 150 community organizations through its CTSA program will be leveraged to promote the *All of Us* Research Program at the community level throughout western Pennsylvania. The VA intends to provide connection to the *All of Us* Research Program through informational/conversational kiosks at various community gatherings and events, in addition to other material relevant to the health of veterans. The program will collect community and participant input through surveys and shared stories. More engagement opportunities will be developed with partners as part of the funding proposal: <https://www.nih.gov/research-training/all-of-us-research-program/funding/all-us-research-program-engagement-partners-ot2>.

12.2.3 Examples of National-Level Engagement Activities

At the national level, we have many dissemination channels for official program materials. Most RMCs have tailored websites that have the capacity for two-way communication. Wondros' *All of Us* Research Program campaign, which will include digital messaging, will be used to engage participants. Targeted special campaigns would also help keep communities of shared interests together. The VA plans to engage well-known, well-respected leaders in the veteran community to discuss the importance of the *All of Us* Research Program to veterans across the country; this approach could be expanded to other national-level communities who are joined by special interest or identity.

12.3 Retention

Long-term retention of participants is by far the greatest challenge to achieving the most ambitious scientific goals of the *All of Us* Research Program. There are several notable examples of successful longitudinal cohort studies with high retention rates over decades, such as the [Framingham Heart Study](#) and the [Nurses' Health Study](#), both with around 90% retention of study participants two to three decades after enrollment. Both of those programs require active involvement by participants only every two years, with the Framingham cohort undergoing an in-person exam and the Nurses' Health Study by mail. The *All of Us* Research Program poses unique challenges relative to these successful examples, well beyond its much greater size. Unlike in Framingham, the participants in the *All of Us* Research Program will be far more geographically diverse, scattered across the United States and U.S. territories, and without the benefit of required recurring in-person visits. The Nurses' Health Study differs in that it is made up of a relatively homogeneous population of individuals with a professional tie to health care, unlike the diversity of backgrounds of participants sought for the *All of Us* Research Program. Due to the scale and geographic spread of the program, retention strategies will be primarily digital but will also include "analog" outreach to ensure retention of the broadest cohort of participants.

12.3.1 Digital Approaches to Retention

A digital retention strategy is made possible by today's ubiquitous connectivity via mobile technologies, including smartphones—which are currently owned by two thirds of all adults in the United States—and personal computers. Due to the scale and geographic range of the program, we anticipate that most long-term interactions with the program will be digital; thus, the web and mobile application have been designed to be user-friendly and engaging, with a responsive and intuitive user interface.

Snap Questions are an example of digital engagement activity designed to enhance participant retention. These are optional multiple-choice poll questions with a view of aggregate responses from other participants and brief relevant facts. Snap Questions are designed to be brief, engaging, and changed regularly.

We will use Snap Questions as one way to attract participants to the Participant Portal to view and complete study-related activities (e.g., new PPI modules, Digital Health Technology activities). We will post three or more new Snap Questions on a health- or wellness-related topic to the Participant Portal at regular intervals, based on participants'

engagement level. At first, we will change the Snap Questions monthly. Every AoURP participant will have the option to respond to the Snap Questions at any time during that month and see how their responses compare to aggregated responses from the rest of the respondents. The Snap Questions will also include a brief fact sourced from public domain trusted information sources (e.g., National Library of Medicine, NIH institutional websites) about that month's health-related topic and how it relates to precision medicine, health, or wellness. Those who wish to learn more will have the option to click on a link to additional information on that topic (viewable on a pop-up window within the portal). This layered approach to the return of information is meant to satisfy participants with different health and reading literacy levels.

Individual-level data will be securely stored on the PTSC database and transmitted to the DRC. The AoURP will use the data for quality improvement to better understand and improve the user experience (e.g., share findings about topics or questions that are most engaging). Aggregate data may be included in program communications, such as in program newsletters or social media channels for participant engagement.

12.3.2 Non-Digital Approaches to Retention

Digital connectivity is not sufficient to establish a high level of retention. For example, the largest experience with mobile device medical research, Apple's ResearchKit, has shown active retention rates of close to only 10% in the months following initial enrollment. Further, non-digital methods will facilitate the retention of those who may not be comfortable with technology. The non-digital methods will include the Support (Call) Center, site-specific touchpoints/services, and other site-specific outreach. The success of long-term retention activities may vary based on the sociodemographics of the region where participants are enrolled. The suite of activities should include methods focusing on multiple levels (individual, interpersonal, community, national). Materials created to engage participants at these levels should be made available to all enrollment sites as best practices.

Non-digital retention strategies successfully employed by other long-term cohort studies include:

- Provision of a small card that has the name of the project with a toll-free contact number that participants can call to update locator information or see information on the project
- Reminder calls to participants to keep them engaged in the project
- Birthday cards to participants from the program; cards would provide the toll-free project number and encourage participants to stay in touch
- Outreach telephone calls to a participant-designated friend or family member (if consented to contact)
- Home visits by trained program staff
- Exit packets
 - Enrollment certificates (recognition)
 - Referral cards for friends and family

12.3.3 Retention Metrics

To measure when, where, and how well retention efforts working inside *All of Us*, we plan to develop metrics for assessing retention over time. Some metrics will be similar across all sites—for example, counting the number of survey modules completed. Other metrics will be specific to subpopulations within the program. For example, for those who download and use the program’s mobile application, we will be able to measure electronic interactions such as login frequency and time spent in the app. Additional retention metrics may include:

- Responsiveness to requests to share additional participant-provided information, indicated by either actively accepting or declining an invitation (electronic or in person)—for example:
 - Invitation to provide routine updates regarding health status
 - Invitation to provide updated contact information as needed
- Responsiveness to communications for involvement in the *All of Us* Research Program by opening or viewing such communications

Additionally, it is recognized that there is no one-size-fits-all retention strategy, so part of the learning process will be how to best individualize retention strategies to best meet the needs of the individual.

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14 List of Terms and Acronyms

Term	Meaning
<i>All of Us</i>	<i>All of Us</i> Research Program
DRC	<i>All of Us</i> Data and Research Center
DV	direct volunteer
EC	<i>All of Us</i> Executive Committee

Term	Meaning
HPO	health care provider organization (RMC, Federally Qualified Health Center, and/or VA)
MEA	<i>All of Us</i> Mobile Engagement Asset
MML	Mayo Medical Laboratories
PMI	Precision Medicine Initiative
PM&B	Physical Measurement and Biospecimen Collection
PPI	participant-provided information
PTSC	<i>All of Us</i> Participant Technology Systems Center
RMC	Regional Medical Center
S4S	Sync for Science
TPC	The Participant Center
UBR	underrepresented in biomedical research

Acronym	Definition
API	application programming interface
BRFSS	Behavioral Risk Factor Surveillance System
EHR	electronic health record
FISMA	Federal Information Systems Management Act
HIPAA	Health Insurance Portability and Accountability Act
IRB	institutional review board
ISIA	Institution-Specific IRB Application
LGBTQ	lesbian, gay, bisexual, transgender, queer
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
SMS	short message service

Acronym	Organization
AHRQ	Agency for Healthcare Research and Quality
BCBSA	Blue Cross Blue Shield Association
CDC	Centers for Disease Control and Prevention
EPA	Environmental Protection Agency
NIH	National Institutes of Health
OCIO	NIH Office of the Chief Information Officer
OHRP	NIH Office for Human Research Protections
OMOP	Observational Medical Outcomes Partnership
OSHA	Occupational Safety and Health Administration
STSI	Scripps Translational Science Institute
USDA	Department of Agriculture
VA	Department of Veterans Affairs