All of Us Research Program Pediatric Protocol

Protocol Title	***All of Us* Research Program Pediatric Protocol**
Principal Investigator(s)	**Paul A Harris, Ph.D.** Vanderbilt University Medical Center +1 615 936-5033
Sponsor	National Institutes of Health (NIH)
Primary Contact	**Sara Van Driest, M.D., Ph.D.** Director of Pediatrics 301-496-6044
IRB reference	**2016-05-Supplement-12-TN-MASTER**
Protocol Version	V1.0
Reference Core Protocol (2016-05-TN-Master)	V1.21

Table of Contents

Table of Tables

Table of Figures

Supplemental Protocol Synopsis

Table 0-1: Protocol Synopsis

TITLE	*All of Us* Research Program (*All of Us* or the program) Pediatric Protocol
SPONSOR	National Institutes of Health (NIH)
FUNDING ORGANIZATION	National Institutes of Health (NIH)
APPROACH	This supplemental protocol is designed to enable pediatric participation in the *All of Us* Research Program. Pediatric participation will be achieved using a phased launch approach. Phase 1 will include enrollment of children from birth to age 4, with participation allowed to continue as they age to 5 and 6 years of age. Thus, participation in Phase 1 will extend from birth through 6 years. Within 2 years of Phase 1, Phase 2 will add the next age group to this protocol; enrollment will be extended from birth to age 10 years, with participation after enrollment through 12 years. Phase 3 will enable enrollment for all ages from birth to adult and add support for participation from age 13 years through the age of majority. Phases 2 and 3 will be added to this protocol by amendment.
ENROLLMENT SITES AND PARTNERS	Each phase will begin with enrollment of a small number of pediatric participants from a small number of currently funded Health care Provider Organizations (HPOs) including Federally Qualified Health Centers (FQHCs), with subsequent expansion to additional sites. For all phases, enrollment awardees will work with awardees representing core functions, such as the Biobank, Data and Research Center (DRC), Genome Centers, Participant Technology Systems Center (PTSC), other technology partners, and community partners.

RATIONALE	As specified by the *All of Us* Research Program, precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by considering individual variability in genes, environment, and lifestyle. Precision medicine research seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through the more precise measurement of molecular, environmental, physiologic, social, and behavioral factors that contribute to health and disease, which in turn will lead to more accurate diagnoses, more robust disease prevention strategies, better treatment selection, and the development of novel therapies. Longitudinal, prospective data from pediatric participants are required to support precision medicine approaches for the young and to enable identification of protective and risk factors early in life affecting health across the lifespan. Data from individuals reflecting the diversity of the United States' (U.S.) population are required for discoveries in precision medicine to advance health equity. Extending enrollment of participants from diverse communities in the *All of Us* Research Program to include individuals under the age of majority (pediatric participants) will increase the scale and scope of research that can be conducted, specifically enabling the research community to develop evidence-based pediatric precision health approaches and to identify presymptomatic biomarkers of health and disease.
STUDY DESIGN	Phase 1 will begin with *enrollment* of children aged birth to 4 years old and *participation* of children aged birth to 6 years old with at least one parent/legal guardian who is currently an *All of Us* Research Program participant. Institutional Review Board (IRB) approval will be required for future phases extending enrollment to enable participation of additional age groups and/or participation of individuals under the age of majority without an associated parent/legal guardian participant. Future phases will be added to this protocol via amendment, with each subsequent phase beginning within 2 years of the prior.
PRIMARY OBJECTIVE	To extend the robust research resource composed of Participant Provided Information (PPI), environmental, physiologic, genetic, and health data plus biospecimens from research participants reflecting the diversity of the U.S. to include individuals under the age of majority. *The All of Us* resource facilitates the exploration of biological, social, and environmental determinants of health and disease and must include the full spectrum of age to adequately reflect the diversity of the population of the U.S.
NUMBER OF PARTICIPANTS AND ENROLLMENT MODES	This protocol (Phases 1–3) will enroll at least 150,000 individuals under the age of majority at the time of enrollment, representing the entire age spectrum (birth–age of majority).

PARTICIPANT SELECTION CRITERIA	Inclusion Criteria for Pediatric Supplement • Currently reside in the U.S. or a territory of the U.S. • Age younger than the age of majority (as defined by the state or territory of residence). • One parent/legal guardian, who is at least the age of majority (as defined by the state or territory of residence), provides permission for enrollment of the pediatric participant, including agreement to provide information about themselves as part of the research program. o Of note, although permission from only one parent/legal guardian is required, if it is known that the child has another parent/legal guardian who opposes participation of the child, the child will not be enrolled. • Pediatric participant provides assent, as appropriate by age and cognitive ability. o Of note, for children of all ages, those expressing active dissent will not be enrolled. Exclusion Criteria for Pediatric Supplement • Children who are or become emancipated minors. • Children who are or become incarcerated. • Children who are or become wards of the state. • Neonates of uncertain viability and nonviable neonates. ADDITIONAL Enrollment Inclusion Criteria for Phase 1 • Age birth through 4 years of age at the time of parent/legal guardian permission. • The (one) parent/legal guardian giving permission must be a current adult participant who has completed primary consent for the *All of Us* Research Program.
DURATION OF PARTICIPATION AND DURATION OF STUDY	**Duration of Study**: The *All of Us* Research Program is expected to last a decade or more. **Duration of Participation**: Participation of those enrolled as part of this pediatric supplement is expected to last for the entire duration of the program, with regular data contribution, age-appropriate permission and assent, and follow-up.
PRIMARY ENDPOINT	Collection and curation of diverse pediatric participant health and derivative biospecimen data to be made accessible to the research community to enable a broad spectrum of research studies.
SECONDARY ENDPOINTS	Building the infrastructure to enroll pediatric participants, collect biospecimens, link data across family members, and securely share health-related data for ongoing research.
SAFETY EVALUATIONS	As in the primary program, safeguards are in place to maintain the privacy of pediatric participants, the confidentiality of the biospecimens, and the security of the data collected through the program (see Core Protocol (2016-05) Section 16: Confidentiality, Privacy, and Security).

Note: Throughout this protocol, the following conventions are used when referring to parents and legal guardians:

- Parent/legal guardian: The singular version used when specifically talking about just one parent or guardian.
- Parent(s)/legal guardian(s): The singular version used when talking about the parent's or guardian's involvement or role in the study. Co-parenting or co-guardianship arrangements may mean multiple people could be interacting with the program for a given child, even if only one person's signature is required on the permission form. See Section 4.5 for more explanation of co-guardianship.
- Parents/legal guardians: The plural version used when referring to all parents or guardians in general.

Section 1: Background and Overview

1.1 Background and Scientific Rationale

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. The *All of Us* Research Program seeks to combine health-related information and specimens from one million or more participants, creating a resource with large scale and inclusive scope to enable research for a wide range of health states to inform precision medicine. The program has employed a thoughtful and inclusive strategy to prioritize groups historically underrepresented in biomedical research (UBR), with the goal of enabling researchers to perform meaningful analyses that could reduce health inequities in and through precision medicine research. Outcomes of this research could include novel prevention and screening strategies, earlier and more precise diagnoses, new and more effective use of therapies, and improved understanding of why some people remain healthy despite exposures and risk factors for disease. The program began with enrollment of individuals over the age of majority (18 years of age in most states and territories) and has been successful in building a diverse adult cohort.

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:

1. Participation is open to all.
2. Participants reflect the rich diversity of the United States (U.S.).
3. Participants are partners.
4. Transparency earns trust.
5. Participants have access to their information.
6. Data are broadly accessible for research purposes.
7. Security and privacy are of highest importance.
8. The program will be a catalyst for positive change in research.

This supplemental protocol codifies guidelines for the inclusion of pediatric participants in the *All of Us* Research Program in a manner consistent with all 8 Core Values, and specifically in alignment with our commitment to Core Values 1 and 2.

The *All of Us* Research Program is an observational research program that aims to provide the information needed for researchers to address a wide range of scientific questions; inclusion of pediatric participants will broaden the spectrum of scientific questions that can be answered. Individuals under the age of majority are underrepresented in research, and resources supporting precision medicine research for infants, children, and adolescents (hereafter “children”) are lacking. Existing resources are limited in sample size, breadth of data collection, ability to share data with the research community, reflection of the diversity of the U.S., and engagement with children, families, and communities. Some examples of opportunities that we anticipate will be enabled by pediatric participation in the *All of Us* Research Program include:

1. Enabling families to participate in research together through family-based engagement, recruitment, and retention activities.
2. Empowering children and their families with information and data provided back to them from the program that may improve their own health.
3. Making pediatric data securely and broadly available to traditional and nontraditional researchers (including community and citizen scientists) to develop innovative technologies and methodologies to improve child health.
4. Developing quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors, and gene–environment interactions, informed by linkages across shared genetics, households, and/or environments across families.
5. Discovering biomarkers that identify individuals with an increased risk of developing diseases, including biomarkers collected prior to onset of any symptoms.
6. Optimizing screening and prevention strategies for pediatric conditions based on individual genomic, environmental, and behavioral risk factors.
7. Developing tools and approaches for new or improved disease classifications and relationships for pediatric conditions.
8. Using digital health technologies to correlate sensor data, behavior, and the environment with health outcomes for children and families.
9. Identifying the determinants of safety and efficacy for therapeutics for children.
10. Using pediatric data to develop new therapeutic strategies for children.
11. Inviting pediatric participants to enroll in ancillary studies, including clinical trials of targeted interventions and therapies.

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. This supplement supports extension of the program to enable collection and curation of health-related data and biospecimens from children reflecting the diversity in the U.S. and enabling the program to reflect the entire spectrum of age; these data and biospecimens will be made broadly available for research uses. This supplemental protocol further defines a phased launch approach for pediatric enrollment; enrollment for Phase 1 will be restricted to pediatric participants age birth through 4 years at the time of enrollment, and to those who have at least one parent/legal guardian who is a current participant in the *All of Us* Research Program. Future phases will extend the age range of enrollment and consider enrollment of pediatric participants without an associated adult participant.

1.2 Protocol Development Activities

The enrollment of children in *All of Us* has been an important goal of the program since its inception. Federal legislators and public interest groups have long worked for the increased inclusion of children in research, and special regulatory protections exist to safeguard their participation in human research. Between 2017 and 2019, *All of Us* staff and consortium members made significant progress on strategic pediatric planning. In 2019, planning for child enrollment within the program was paused to prioritize diversity of adult enrollment before

doing so for children. Pediatric efforts were restarted in 2020, resulting in the drafting of the Pediatric Playbook and hiring of the Director of Pediatrics in 2022. The Director of Pediatrics guided the drafting of this supplemental protocol, building upon the significant prior efforts detailed below around planning, strategizing, and conceptualizing pediatric inclusion in the *All of Us* Research Program.

In 2016, the *All of Us* Research Program established the Child Enrollment Scientific Vision Working Group (CESVWG). It was a working group of the *All of Us* Advisory Panel formed to develop the approach for including pediatric populations. The CESVWG identified critical research that *All of Us* may be uniquely positioned to enable through enrollment of children from diverse backgrounds into the *All of Us* cohort in their December 2017 report.[1]

The Pediatric Scientific Vision Task Force (PSVTF), comprising *All of Us* consortium members with various pediatric subject matter expertise, was established in December 2017 and was charged with delivering a final report assessing the practical and logistical considerations of the scientific opportunities identified by the CESVWG. The May 2018 PSVTF report built upon the four major research themes identified by the CESVWG. Those themes include consideration of multiple influences on health status, primary prevention, resilience, and family context across the lifespan incorporating intergenerational perspectives.

The Pediatric Operations Task Force (POTF), comprising *All of Us* consortium members with various pediatric subject matter expertise, worked from 2018–2019 to identify modifications needed to the Core Protocol to enable the enrollment of children in *All of Us*. With the support of *All of Us* program leadership, the POTF successfully defined the pediatric age groups, began work to define the physical measurement and biospecimen (PM&B) plan for children, and created a Pediatric Participant Provided Information (PPI) task force. The Pediatric PPI task force developed the concepts for the Basics PPI modules for each child age group. The POTF recommended the phased launch approach, beginning with the youngest age group.

After pausing pediatric efforts in 2019 to focus on other program activities, the *All of Us* Research Program convened a team of program staff to develop the Pediatric Playbook in 2020, with the intent to officially capture all program progress on child enrollment prior to 2019 and to outline the strategic approach to enroll children in the program. The vision laid out in the Pediatric Playbook for pediatric enrollment is to enroll and retain at least 150,000 children ages birth to age of majority who reflect the broad and rich diversity of the U.S. population. There is no upper limit on enrollment as the goal to build a robust research resource is not dependent upon reaching any statistically determined sample size.

Throughout these efforts, the program conducted a series of child ecology modeling and focus groups to research and understand parents' needs, motivations, and goals regarding their child's potential participation in the program. Information garnered from these child ecology modeling sessions informs pediatric recruitment engagement and retention strategies for children.

1.2.1 Community Engagement in Protocol Development

Pediatric Enrollment Listening Sessions: The program hosted multiple engagement studios with community members and sessions with the *All of Us* Participant Ambassadors on pediatric enrollment. These studios and sessions presented an opportunity for feedback from current adult

participants and community members on pediatric enrollment in *All of Us* with a particular interest in the perspectives of those who care for children.

Common feedback from community members:

- Trust is vital and must be earned and maintained (over time)
- Representation of diverse communities across all aspects of the program, such as on governing bodies (as appropriate), is important
- Referral by trusted sources and health providers is needed and may increase enrollment
- Creative approaches will be required to engage parents/legal guardians and children
- Messaging should be tailored specifically to families, parents/legal guardians, and children
- Before and throughout the journey, thoroughly explain and educate on the process to enroll and participate
- Regarding return of value, the needs of community should be considered; participants want to feel valued and to understand tangible benefits both short and long term for their children

Key informant interviews with pediatricians and pediatric health care providers also occurred to inform the program on topics of enrollment, return of results, and research from a health care provider's perspective.

Future community engagement studios on the topic of pediatric enrollment will add to the information already available from previous engagement studios on the same topic, providing an iterative process with more communities and allied health professionals across the country.

In addition to these studios, the program will also fund partners to conduct outreach and engagement with a focus on specific pediatric populations. *All of Us* has identified current partners, such as Stanford University/PRIDEnet, National Alliance for Hispanic Health (NAHH), American Association on Health and Disability (AAHD), and Delta Research Educational Foundation (DREF), that are well equipped to engage future pediatric participants, their family members, and community stakeholders to facilitate engagement across the lifespan. For example, Stanford University/PRIDEnet, will conduct at least one community listening session to generate Sexual Gender Minority (SGM) parent-focused and/or adolescent-focused recommendations. AAHD provided critical feedback on definitions and assessment of disability status for pediatric participants and will continue to provide guidance for engagement and enrollment of children with special health care needs. Working with our community engagement partners, the *All of Us* Engagement Core will coordinate the inclusion of diverse individuals to represent, champion, and inform pediatric and family activities through existing program governance and establishment of the *All of Us* Youth and Family Committee to ensure specific inclusion of young people and parents/legal guardians from diverse communities. NAHH and DREF will engage children and their families from Hispanic/Latino and African American/Black communities, respectively, through various activities. Additional partners who will facilitate direct input from older children and adolescents regarding pediatric participation in the *All of Us* Research Program will continue to be identified.

1.3 Phased Implementation of Protocol

1.3.1 Phased Launch Rationale

For the *All of Us* Research Program to follow the program's Core Value #1 ("Participation is open to all"), enrollment must be expanded to the full spectrum of ages. Throughout infancy, childhood, and adolescence, there are profound periods of growth and developmental change. Engagement, enrollment, and retention of pediatric participants across the age spectrum requires age-appropriate strategies for interaction with the child and their family. For every age group, *All of Us* participation has significant ethical, legal, practical and technical considerations. In addition, the relevant data to support scientific advances gathered from the pediatric participants and their families differ across life stages. Given these changes over time, the phased approach enables development of a protocol and procedures for each age group. The three POTF-recommended age groups (birth to 6 years, 7–12 years, and 13 years to age of majority) support age-appropriate research design.

Importantly, the phased launch approach supports the development of a robust dataset for pediatric precision health research in the near and long terms, with representation across the pediatric age span. The accelerated longitudinal design,[2] after all phases are complete, will allow for enrollment of children at any age, with subsequent longitudinal data collection. In comparison to a birth-cohort longitudinal design, allowing enrollment at any age enables accelerated data capture across the entire age spectrum, enabling the use of strategies such as cross-sectional analysis, latent growth modeling, and cross lag analysis, until traditional longitudinal data are collected.

Consistent with the POTF recommendation, Phase 1 will focus on the youngest age group (birth to 6 years). There are several important reasons for this approach. The primary consideration is the scientific value of the data accrued by the program over time, which is maximized by beginning enrollment as early in life as possible. This, and additional rationale for beginning with the youngest age group, are as follows:

- Scientific: Beginning enrollment with the youngest pediatric participants facilitates active data capture beginning early in life with the potential for the best longitudinal follow-up from infancy/childhood into adulthood as the cohort (and each pediatric participant) matures. While retrospective survey and electronic health record (EHR) data have the potential to provide information regarding infancy and early childhood for participants who enroll later in life, survey data are subject to recall bias, and EHR data may be incomplete or unavailable (e.g., if the pediatric participant has a new health care provider).
- Programmatic: We intend to enroll all age groups, and it is not pragmatic to enroll all ages at once, because different age groups have different enrollment requirements. Beginning enrollment with the youngest pediatric participants allows *All of Us* to better incorporate the feedback previously obtained and currently being gathered from parents/legal guardians, who have spoken on behalf of their infants and young children (as is appropriate for this age group). Work has begun to enable *All of Us* to obtain input from older children or adolescents and to include young people on program governance bodies, as appropriate. Engagement of and guidance from older children and adolescents

prior to beginning enrollment will better inform later phases (i.e., Phase 3, anticipated to be initiated within 2–4 years of Phase 1) focused on older children and adolescents.

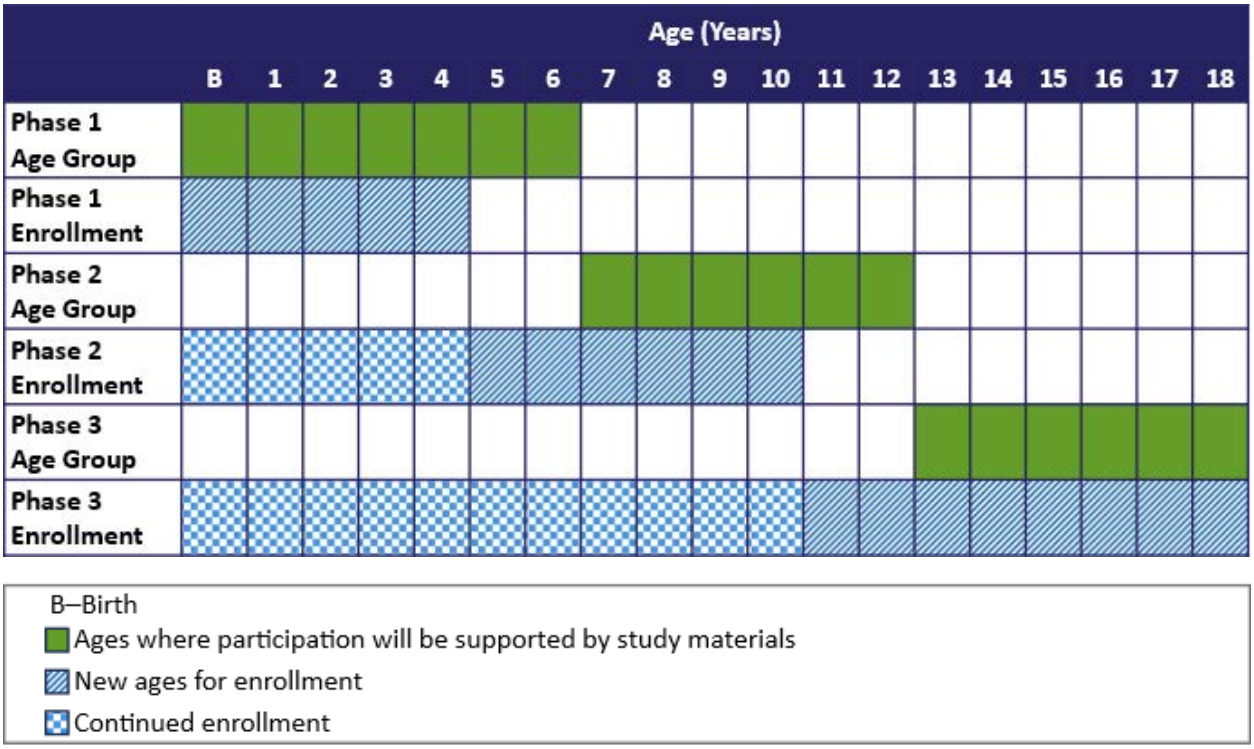
- Technical: Because the enrollment of the youngest children will rely on interactions with parents/legal guardians, enrollment of this age group will most closely match the current Core Protocol (2016-05) and procedures. This youngest age group is not a population of convenience. Rather, the selection is purposive, beginning with infants and young children allows *All of Us* to leverage its current infrastructure and start enrolling while continuing to obtain input from older children and adolescents. New features to allow both the parent(s)/legal guardian(s) and the pediatric participant to interact with the program, as appropriate by age, will be developed for older age groups in later phases.
- Ethical: There are important ethical considerations for every age group. The phased approach, beginning with the youngest children, allows the program to focus on this age group where considerable ethical, legal and social implications (ELSI) research and experience is available.
    - Although clinical research involving children routinely begins enrolling adolescents first and working down to younger age groups, the ethical precept of conducting research first with adolescents before including younger children does not add any substantive protections for observational, longitudinal studies like *All of Us*. In clinical research, enrolling adolescents first functions as a risk mitigation strategy because adolescent physiology is similar to adult physiology and the adolescent is better able to communicate adverse effects (and ostensibly to comprehend and assent to the potentially greater risks of the research). For *All of Us*, there is no clinical intervention, and the risks of this research are largely consistent across the lifespan. Further, it is unlikely that lessons learned from enrolling adolescents would translate to younger age groups or improve their experience in meaningful ways, and enrolling the youngest cohort first allows the program to learn from the experience of these children in the program as they age.
    - As this is an observational research program rather than a clinical trial, there are no special burdens of research (i.e., risks) being placed on the youngest children. Balancing respect for persons with considerations of justice and beneficence, the program began research with enrollment of adults before children, non-institutionalized persons before institutionalized persons, and persons with decisional capacity before persons without that capacity. Justice and beneficence considerations however also informed the program's decision to offer the research opportunity first to the youngest children, who are most frequently excluded, and to maximize the potential for benefit from research participation while minimizing risks.
    - Respect for persons is shown by offering children the opportunity to exercise their growing autonomy, by giving assent at several time points as they grow older and mature (e.g., at age 7 and 13). Even though young children may not be capable of assent, the program will show respect for them by explaining what will happen at an age-appropriate level and honoring active dissent at any age. As the child ages, they will have the opportunity to withdraw. Since engaging and listening to older children and adolescents prior to enrolling these age groups will enable the

program to gain a deeper understanding of their perceptions about potential benefits and risks of participation, we will be in a better position to maximize potential for beneficence and show respect to pediatric participants by supporting their growing autonomy and ability to make informed choices for themselves.

- Legal: There are important legal considerations for every age group. The program is now in a position to satisfy the legal considerations for the youngest age group. For the oldest age group, there are additional considerations (e.g., privacy, reaching age of majority, emancipated minors, etc.) that will be addressed in future phases.
- Regulatory: There are no regulatory requirements to begin research with one age group over another.

Figure 1-1 depicts the age groups for protocol development for each phase, as well as the anticipated ages of enrollment at each phase. Of note, for Phase 1 and Phase 2, the maximum age of enrollment will be 2 years less than the focus age group (e.g., for Phase 1, we will enroll birth through 4 years of age), allowing time for development of age-appropriate procedures and materials for participation as pediatric participants age.

Figure 1-1. Age Groups and Anticipated Ages of Enrollment for Phases 1, 2, and 3



Materials for the implementation of each phase of this pediatric protocol will be submitted to the IRB as amendments to this supplemental protocol in stages as they are developed. *Section 16: Table of Future Pediatric Protocol and Core Protocol Appendix Amendments* shows planned protocol content and appendices that will be provided to the IRB in future submissions.

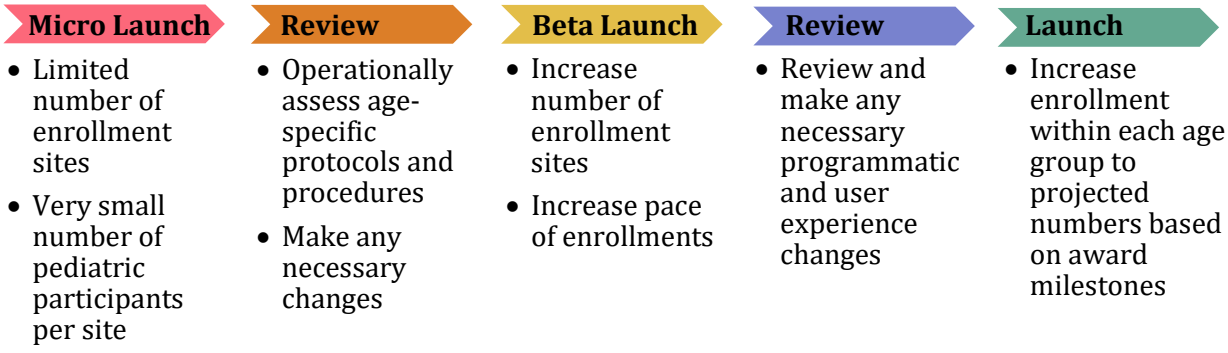
1.3.2 Implementation Stages for Each Phase

The *All of Us* Research Program will use a staged approach to implement each of the three age-group based phases (see Figure 1-2). After development and approval of all materials necessary for each phase and programmatic end-to-end testing of systems and procedures, enrollment will begin with a micro-launch. The goal of the micro-launch is to further assess the practicality, function, usability and interoperability of systems and procedures with pediatric participants and their parents/legal guardians in "real world" environments. A small number of existing enrollment sites (e.g., 1–5 sites) reflecting characteristics of future enrollment sites will be involved. Each site will enroll a small number of participants (e.g., 1–5 pediatric participants), after which micro-launch enrollment will be paused for a post-micro-launch review. The review will be specifically tailored to the needs of each micro-launch and will critically examine the pediatric enrollment experience by analyzing the following types of data: feedback pertaining to the enrollment experience, uptake, error rates and completion times on enrollment activities such as permissions module(s), PPI completion, and PM&B, and/or feedback on why a parent/legal guardian does not choose to enroll their child. These data will be collected during and after the implementation of each phase (i.e., micro-launches for Phase 1, 2 and 3). The post-micro-launch reviews are done with the goal of identifying necessary changes and desired enhancements; changes requiring IRB review will be submitted in amendments to the IRB prior to implementation.

After implementation of changes identified by the post-micro-launch review, the phase will enter a beta-launch stage. The goal of the beta-launch is to assess scalability and further inform user experience. Approximately 200 pediatric participants per site will be enrolled, followed by a pause in enrollment to enable post-beta-launch review. Necessary changes will be made prior to full programmatic launch of the phase, during which the sites will be permitted to enroll consistent with their milestones and goals.

Of note, once micro-launch for each phase is complete, additional sites may be added. Each new enrollment site will proceed through similar micro- and beta-launch stages to assess the local implementation of and participant/parent/legal guardian response to protocols and procedures prior to full-scale implementation of pediatric enrollment.

Figure 1-2. Anticipated Implementation Stages for Each Phase



1.3.3 Phase 1: Birth to Age 6 Years

Phase 1 will involve the participation of children in the age range of birth through 6 years. However, the program will only actively enroll children in the age range of birth through 4 years at the time of enrollment. This will allow time for the development of age-appropriate materials for Phase 2 before enrolled children turn 7 years old. Children 5–6 years of age will not be actively enrolled until Phase 2 is launched. Children enrolled at a younger age may continue as pediatric participants in the program as they turn 5 and 6 years of age.

Additional Phase 1 Inclusion Criteria:

- Age birth through 4 years of age at time of parent/legal guardian permission
- The (one) parent/legal guardian giving permission must be a current adult participant who has completed primary consent for the *All of Us* Research Program
    - Of note, although permission from only one parent/legal guardian is required, if it is known that the child has another parent/legal guardian who opposes participation of the child, the child will not be enrolled.

Since Phase 1 has the additional eligibility criterion of having one parent/legal guardian as a participant in the *All of Us* Research Program, effective enrollment strategies may include, but are not limited to, those that specifically reach current adult participants. If the parent/legal guardian who is a current adult participant withdraws their own participation in the *All of Us* Research Program, the pediatric participant will be deactivated (parent-/legal guardian-facing term "paused" to help indicate the child may resume participation in the future if they meet eligibility requirements again); withdrawal and deactivation are further described in Section 8.

Consistent with the staged launch process, Phase 1 will begin with a micro-launch with 5 or fewer existing HPO and/or FQHC enrollment sites that have existing children's hospitals and community sites providing pediatric care making it feasible to begin with current awardees rather than bringing in new sites. Selection criteria for these sites is based on site characteristics including prior success in meeting enrollment and diversity goals for adults, prior success in enrolling through family-relevant sites such as obstetrics/gynecology clinics, ability to support necessary research activities for pediatric participants, and ability to provide EHR data on the enrolled children and paired adult participants. Micro-launch and beta-launch stages, each followed by review, will precede full launch, with an anticipated timeline of approximately 6 months from one stage to the next. Expansion beyond HPO-based enrollment to self-guided participation will occur when pediatric participation can be supported in this fashion.

1.3.4 Phase 2: Ages 7 to 12 Years

After Phase 1, Phase 2 will implement the procedures, processes, and materials to enable participation of children aged 7 to 12 years. Enrollment criteria will be expanded from birth through 4 years to birth through 10 years of age at the time of enrollment (including 5- and 6-year-olds). Phase 2 will also include procedures for obtaining assent from pediatric participants who enrolled prior to age 7, reach 7 years of age, and wish to continue to participate in the program. Enrollment sites for Phase 2 will include Phase 1 sites, with initial enrollment restricted to a small number of sites for approximately 6 months (micro-launch), followed by beta-launch, similar to Phase 1. Additional sites may be added to achieve enrollment goals.

1.3.5 Phase 3: Age 13 Years to Majority

After Phase 2, Phase 3 will implement the procedures, processes, and materials to enable participation of children aged 13 years to the age of majority in their state or territory of residence. Criteria for age at the time of enrollment will be expanded from birth through 10 years to birth through age of majority, including 11- and 12-year-olds. Phase 3 will include procedures for obtaining re-assent from pediatric participants who enrolled prior to age 13, reach 13 years of age, and wish to continue to participate in the program. It will also include procedures for obtaining consent from pediatric participants who enrolled prior to the age of majority, reach the age of majority, and wish to continue to participate in the program as an adult. Enrollment sites for Phase 3 will include Phase 1 and 2 sites, with initial micro-launch and beta-launch stages, similar to Phases 1 and 2. Additional sites may be added to achieve enrollment goals.

1.4 Program Overview

Eligible pediatric participants whose parent(s)/legal guardian(s) provides permission, and who provide assent to take part in the program (depending on age) are invited to share their EHRs and answer health-related surveys. Pediatric participants will also be invited to provide physical measurements and biospecimens from which genomic information and other biomarkers will be derived. The data and biospecimens collected will become a useful resource for current and future researchers.

The program is conducted in accordance with the Belmont Report and the Federal Common Rule (45 CFR 46). The Core Protocol's return of health-related DNA results activities are conducted in accordance with 21 CFR 50, 56 and 812, but these activities are not yet included in the pediatric protocol. The Core Protocol, this supplement, and any pilots or additional supplemental protocols started under the Core Protocol, are subject to the pre-2018 Common Rule. Projects related to the program undertaken outside of the Core Protocol and implemented after January 21, 2019, are subject to the 2018 Common Rule.

1.5 Creating a Resource for Pediatric Research, Focusing on Four Key Domains

The pediatric stage of human development is one of unparalleled growth and development. While it is generally acknowledged that the exposures and experiences from birth to age 18 years significantly impact adult outcomes, the specific mechanisms of how and why this occurs are not well understood. As such, life-course research offers the opportunity to illuminate clues about early roots of disorders, developmental progression of wellness and disease, differential manifestation of disease across the lifespan, and methods to identify individuals at risk in early stages of diseases and disorders. As identified by the PSVTF and refined in the Pediatric Playbook, there are four interrelated scientific research areas that *All of Us* is uniquely suited to address through enrollment of pediatric participants: **(1) pediatric health disparities; (2) physical environment and exposures; (3) family environment and social experiences; and (4) biomarkers.** This supplement focuses data collection and research design on these four scientific areas.

As described below, inclusion of pediatric participants in the *All of Us* Research Program will enable scientific advances benefiting children and families across all four scientific focus areas. Equipped with the resulting data, researchers will have the opportunity to explore questions

including but not limited to effects of evolving social and physical environments on pediatric health, periods of heightened pediatric vulnerability, adult disease antecedents, and gene-environment interactions (GxE). Researchers will be enabled to widen the lens on presymptomatic features of pediatric disease, build normative ranges for a variety of pediatric biomarkers, and examine the role of pediatric health disparities leveraging a range of biomarkers. The *All of Us* pediatric cohort will be a premier data source to inform the future of pediatric precision health for years to come, with a focus on inclusion of diverse populations to reduce health disparities.

1.5.1 Pediatric Health Disparities

Health disparities begin early in life,[3] and the PSVTF acknowledged this when it ranked pediatric health disparities as the single most important scientific area of focus for the pediatric program. Life course research demonstrates that disparities in health during childhood are associated with long term risk of chronic illness, increased severity of disease in inherited disorders, and reduced life expectancy.[4] While numerous cross-sectional and longitudinal cohort studies are designed to focus on or include evaluation of disparities, there is no longitudinal study focused on characterizing origins of health disparities in the U.S. population[5,6] that is similarly-sized and similarly diverse (both demographically and geographically) to the *All of Us* Research Program.

In addition to its rich diversity and large sample size, there are at least three strengths that uniquely position the *All of Us* Research Program to make substantial contributions to pediatric health disparities research. As outlined by the PSVTF, these strengths include the "opportunity to explore and confirm hypotheses about the multifactorial nature of health disparities, the opportunity to examine these hypotheses across the life course, and the ability to develop or support new hypotheses about primary prevention, resilience, and the risk of disease across generations."

Being a catalyst for positive change in research (Core Value #8) is paramount as the program formulates its strategy for addressing health disparities in conjunction with enrolling and retaining a diverse pediatric cohort for decades to come. Principles of structural competency, which recognize that health care providers and systems can only provide optimal health care to individuals by understanding their lived experiences and changing policies and structures to overcome barriers to care, are rarely systematically evaluated or prioritized in the current U.S. health care system or research studies. The *All of Us* Research Program can play an integral role in providing a robust dataset that takes into account a broader range of experiences and health influences.

Since health disparities are multifactorial, the program will employ a biopsychosocial approach to data collection and the development of research questions, examining biological and clinical data alongside data from physical and social environments. As noted by the PSVTF, the overarching vision related to pediatric health disparities is that "collection of data from each of these domains could lead to a better understanding of how social and structural factors (access, education, poverty) interact with those biological processes (neuroendocrine, autonomic, immune) often found to be associated with poor health outcomes in low income and vulnerable populations."[7] Within this vision, myriad scientific questions are ripe for exploration; some of the most relevant pediatric research areas and questions, based on recommendations from the CESVWG and other pediatric stakeholders, are listed in Table 1-1.

Table 1-1. Sampling of Research Opportunities for the *All of Us* Pediatric Cohort

Pediatric Health Disparities

Topic Area	Potential Research Questions for *All of Us*
Early health outcomes (and the association of these outcomes with low socioeconomic status, race/ethnicity, discrimination, poor housing, etc.)	Does a prolonged period of social disadvantage or discrimination harm the children and grandchildren of marginalized and vulnerable groups, creating a cycle of poor health outcomes?
Periods of heightened health vulnerability	Are there periods of pediatric growth and development that are most sensitive to environmental or social insults?
Adult disease antecedents	Are there certain physical or clinical measures such as cortisol levels or blood pressure indicating harmful levels of stress that could be precursors to adult disease?

Physical Environment and Exposures

Topic Area	Potential Research Questions for *All of Us*
Early health outcomes (and how these relate to parental health, exposure history, behaviors, etc.)	How might parental biology, exposures and experiences from childhood through adulthood influence the early health outcomes of their offspring? [a]
Evolving physical environments	Are adverse living conditions in early childhood (e.g., poor nutrition, environmental toxins, or emotional duress) related to increased or sustained rates of asthma morbidity, cardiovascular disease and psychiatric disorders in adulthood?
Gene-environment interactions (GxE) [b]	How might common and rare genetic variability within pediatric populations contribute to susceptibility to disease or resilience throughout the life course?

[a] Though further research will likely reveal many additional parental experiences that impact birth outcomes of their offspring, experiences of racism is one that can contribute significantly to health disparities. For Black women, maternal lifetime exposure to interpersonal racism is associated with risk of very low birthweight across measured sociodemographic, biomedical and behavior characteristics. Experiences of vicarious, or witnessed, racism, are associated with adverse health outcomes, especially socioemotional and mental health outcomes. See National Center for Health Statistics. *Health, United States*, 2015: With Special Feature on Racial and Ethnic Health Disparities. Hyattsville, MD. 2016.

[b] GxE studies are particularly important when examining the development of complex traits and pathways to disease or resilience in pediatric populations. Certain analyses are currently being conducted with adult data from the UK Biobank dataset using genome-wide association studies (GWAS), with significant findings in multiple areas of physical and mental health including obesity, multiple sclerosis, coronary heart disease, inflammation, depression, schizophrenia, and ADHD. The program will provide an unprecedented opportunity to examine the development of such concerns in a large and diverse sample of children using both longitudinal and cross-sectional analyses.

Family Environment and Social Experiences

Topic Area	Potential Research Questions for *All of Us*
Evolving social environments	• How do evolving social environments (peer interactions, experiences of racism, adverse childhood experiences (ACEs), etc.) from birth-childhood-adolescence impact mental health and wellbeing across the lifespan? • What role does family structure have on children as they age?

Biomarkers (Genetic and Non-Genetic)

Topic Area	Potential Research Questions for *All of Us*
Normative trajectories of change; primary prevention	• Are there (genetic, non-genetic, or digital) biomarkers apparent during childhood, in the general population, that predict future disease? • What biomarkers during childhood predict resilience/competence in high-risk groups? • Are there biomarkers that measure how children react to different exposures or interventions?
Reference ranges	What are the appropriate reference ranges for pediatric biomarkers of hematology, hepatology, endocrine function, immunology/renal function, etc.?
Genetic predispositions to disease and therapeutic response	• How might common and rare genetic variations influence a child's predisposition to disease in childhood and in adulthood? • How might genetic variations influence a child's response to a variety of therapeutics?
External recruitment	How might the pediatric efforts within the *All of Us* Research Program support existing research related to biomarkers and disease?

1.5.2 Physical Environment and Exposures

Assessing the physical environment and exposures of pediatric participants plays a critical role in examining the multifactorial nature of health disparities introduced above. The *All of Us* Research Program plans to enroll pediatric participants from diverse environmental and familial backgrounds to examine how family structure, genetics, and environmental exposures impact health outcomes, enabled and accelerated by data collection from surveys, biospecimens, digital devices, electronic health records, and data linkages.

One growing area of research to which the program is poised to make significant contributions involves the study of GxE on children's well-being; GxE studies are particularly important when examining the development of complex traits and pathways to disease or resilience in pediatric populations. It is known that genetic variability contributes to susceptibility to diseases.[8] Such

analyses are currently being conducted with adult data from the *All of Us* Research Program and other large cohorts using genome-wide association studies (GWAS), with significant findings in multiple areas of physical and mental health including obesity, multiple sclerosis, coronary heart disease, inflammation, depression, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD).[9] The program will provide an unprecedented opportunity to examine the development of such conditions in a large and diverse sample of children using both longitudinal and cross-sectional analyses.

Another area of research that the program may make significant contributions to includes environmental exposures. Determination of survey data on environmental exposures from parents/legal guardians will leverage already validated and tested items and scales from existing data sources or tools such as Environmental influences on Child Health Outcomes (ECHO), the National Children's Study, National Survey of Children's Health, Centers for Disease Control Q-Bank, or NIH PhenX Toolkit and may be supplemented by data linkages. Pediatric survey modules will be constructed to maximize scientific value and validity as well as ease of use by parents/legal guardians and, when appropriate, by the pediatric participant.

1.5.3 Family Environment and Social Experiences

In addition to studying the impact of environmental exposures during the pediatric period, the program recognizes that family environment and social experiences are critically important given what we have begun to learn about social determinants of health, resilience, and the interaction of the environment with experiences of children and their families. As the CESVWG noted, "the potential of the *All of Us* Research Program to enroll multiple individuals from the same family with known relationships may enable research to assess family functioning, family aggregation of disease, and transmission of health and disease to new families."[10]

The program recognizes the multifactorial nature of pediatric health and will thus take a biopsychosocial approach to data collection. Family environment and early social experiences form a significant part of pediatric psychosocial data. The program sought and will continue to seek guidance from community, scientific, and programmatic stakeholders in defining family, including socio-cultural norms and practices related to family structures and decision-making, and developing strategies for data sharing within families. The implementation of these strategies has major impacts on pediatric participant engagement, enrollment, and retention. Effective strategies are also required to ensure the data are high quality, enabling research related to social determinants of health. Indeed, the opportunity to analyze intersecting and layered *All of Us* adult and pediatric data will be a unique and profound offering of the *All of Us* Research Program to pediatric research communities and those they serve.

1.5.4 Biomarkers

In 1998, biomarkers were defined by the NIH Biomarkers Definitions Working Group as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[11] Within the *All of Us* Research Program's pediatric cohort, biomarker collection, including biospecimens for genetic analysis, will complement studies of health disparities and environmental/social experiences by allowing inferences to be made regarding biological pathways that result from experiences and exposures. Additionally, this will enable generation of

preliminary data that can be validated and used for intervention studies intended to reduce health disparities. Biospecimens collected from children enrolled in the *All of Us* Research Program will give pediatric researchers a unique opportunity to study a range of exposures and biological data in both cross-sectional and longitudinal studies, enabling a broader understanding across various domains, from polygenic risk scores to pharmacogenetics to disease predispositions. In this way, biomarkers are viewed by the program as an enabling platform to address a variety of highly valued scientific questions.

The PSVTF indicated that biomarker data is at the forefront of translational pediatric research efforts. For many biomarkers, there is no standard for children of different ages and little information about normative trends or individual differences in trajectories as children grow. In the context of prioritizing health disparities, biomarkers that reflect biological pathways of social and environmental stressors are critically important for future studies of interventions that may mediate consequences of a host of factors that impact adverse health outcomes, such as adverse childhood experiences. Collection of biospecimens across the pediatric age spectrum, coupled with longitudinal participant-reported and EHR data, will enable broad research opportunities, including exploration of interactions of genetics with the environment, social determinants of health, and other aspects of wellbeing.

Biomarkers represent a rich opportunity not only for researchers to support improvements in child health and reductions in health inequities, but also an opportunity for pediatric participants to engage with the program. In a series of focus groups aimed at understanding the perceived value of pediatric participation in the *All of Us* Research Program, parents/legal guardians consistently indicated that gaining meaningful insight into predispositions for their children would be highly valuable and would encourage them to partner with the program long term. In addition, they indicated interest in biomarkers providing opportunities to study and deliver value related to pharmacogenetics, or the interplay of genetics and drug response within pediatric populations. Genetic return of results has potential to be a strong driver of pediatric enrollment and retention. In addition, currently over 95% of participants in current GWAS are of European descent. The *All of Us* Research Program is committed to building a cohort reflecting the diversity of the U.S. This diverse cohort has the potential to create a watershed resource for the global public health community.[12] Given the evolving social, ethical, and regulatory implications of delivering actionable genetic information to parents/legal guardians and children across the pediatric period, we are currently developing a plan for responsible delivery of genetic information to pediatric participants and their families. The approach used to develop the genetic return of results plan and the delivery itself are consistent with the program's Core Values #3 and #5 ("Participants are partners" and "Participants have access to their information"). The plan for genetic return of results for pediatric participants and their families will be provided in an upcoming amendment to this protocol and relevant appendices.

1.6 Program Timeline/Program Duration

The *All of Us* Research Program is expected to last decades, with active enrollment occurring until we reach enrollment goals. Follow-up is expected to be continuous for the life of the program. Pediatric participation is expected to continue for the duration of the program. The data analysis platform (the *All of Us* Research Hub) is available for public use, including the collected pediatric and family data, with qualified researchers registering for additional data access.

Section 2: Selection of Participants

2.1 Eligibility

As with the current adult-focused protocol, pediatric efforts in the *All of Us* Research Program seek to engage diverse populations of the U.S. in terms of demographics, health status, disabilities, and geography. This includes enabling all individuals meeting the inclusion/exclusion criteria and living in the U.S., or a territory of the U.S., to enroll, with appropriate consent, permission, and assent processes in place.

There are specific opportunities and challenges of enrolling a diverse pediatric cohort. Qualifiers of diversity include but are not limited to race, ethnicity, sex, gender identity, sexual orientation, disability status, access to care, income, educational attainment, and geographic factors; age interacts with several of these qualifiers. The current program actively recruits populations who are historically underrepresented in biomedical research (UBR). The emphasis placed on UBR groups is an effort to enable rigorous, equitable research that may inform policy, prevention, and/or treatment approaches and thereby decrease current health disparities and inequities. This emphasis is retained in the pediatric supplement and in work by the pediatric program.

Educational content and permission and assent materials are developed in English and Spanish; therefore, initial enrollment efforts are focused on pediatric participants and/or family members who read and speak either English or Spanish. Translated materials are generated through an IRB-approved translation procedure (Appendix P) and provided to the IRB for their records.

Additionally, we will ensure participation is open to persons living with disabilities. Site-specific accommodations will be made to ensure that persons living with disabilities who meet the inclusion criteria are able to enroll. Pediatric participants may be enrolled prior to or after the manifestation or diagnosis of a disability. For more about enrollment of pediatric participants with cognitive disabilities, see Section 4.7.8.

2.2 Inclusion and Exclusion Criteria

The *All of Us* Research Program accepts all potential pediatric participants who meet the eligibility criteria. See Section 1.3 for additional Phase-specific eligibility criteria.

2.2.1 Inclusion Criteria for the Pediatric Supplemental Protocol

- Currently reside in the U.S. or a territory of the U.S.
- Age younger than the age of majority (as defined by the state or territory of residence).
- One parent/legal guardian, who is at least the age of majority (as defined by the state or territory of residence), provides permission for enrollment of the pediatric participant, including agreement to provide information about themselves as part of the research program.
    - Of note, although permission from only one parent/legal guardian is required, if it is known or if the program learns that the child has another parent/legal guardian who opposes participation of the child (i.e., if another parent/legal guardian notifies the program), the child will not be enrolled.

- Pediatric participant provides assent, as appropriate by age and cognitive ability.
    - Of note, for children of all ages, those expressing active dissent will not be enrolled (see Section 4.4.2).

2.2.2 Exclusion Criteria

Until specific enrollment procedures are developed, the following individuals are excluded:

- Children who are or become emancipated minors.
- Children who are or become incarcerated.
    - Incarceration means involuntarily confined or detained in any kind of penal institution, such as in a juvenile detention center, or in an institution for treatment of psychiatric illness or substance abuse as a form of sentencing or alternative to incarceration.[13]
    - The following types of individuals are not incarcerated and therefore are still eligible for enrollment:
        - Individuals who are receiving non-residential court-ordered substance abuse treatment and are residing in the community.
        - Individuals who have been voluntarily admitted to an institution for treatment of a psychiatric illness, or who have been civilly committed to non-penal institutions for treatment because their illness makes them a danger to themselves or others.
        - Persons living in the community and sentenced to community-supervised monitoring, including parolees.
- Children who are or become wards of the state.
- Neonates of uncertain viability and nonviable neonates (i.e., neonates will only be enrolled if they are viable, defined by 45 CFR 46.202(h) as able, after delivery, to survive, given the benefit of available medical therapy, to the point of independently maintaining heartbeat and respiration).
    - Of note, neonates (newborn infants) are a regulated vulnerable population under 45 CFR 46 Subpart B, and only viable neonates are eligible. The enrollment of children older than newborns is not conditioned upon health status or anticipated mortality.

Of note, just as the current Core Protocol does not intend to enroll prisoners without IRB approval, the pediatric supplemental protocol does not intend to enable enrollment of children who are incarcerated or children who are wards of the state. See Sections 4.7.5 and 4.7.6 for more information.

Section 3: Recruitment Outreach

3.1 Recruitment Outreach

To achieve the broad enrollment objectives of the *All of Us* Research Program, *All of Us* engages prospective participants through a range of outreach approaches. Outreach is defined as providing materials and information about the program in advance of creating an *All of Us* account. Currently, prospective participants learn about the *All of Us* Research Program via advertisement, personal interest groups, and directly at partner sites. Specific outreach approaches for pediatric and family enrollment are provided in the communications appendices (Appendix C and Appendix D series). Outreach approaches and materials for the youngest pediatric participants (e.g., infants and toddlers) will be directed to parents/legal guardians, not to children. Outreach materials may be developed specifically to reach older children in later phases. These outreach materials will require IRB review in a future amendment and will go through a review process determined by the *All of Us* Division of Communications and the IRB.

IRB-approved assets, including brochures, flyers, other advertisement messages, images, videos, and other outreach content specifically developed for pediatric and family inclusion into the program, will be accessible on the *All of Us* Communications Portal (https://www.allofuscomms.org/). Consistent with the current Core Protocol, assets developed for pediatric and family inclusion may be combined and personalized with other pediatric/family assets for various populations (e.g., rural, location, etc.) as long as the composite assets maintain the approved standards endorsed by the IRB. Pediatric/family assets will not be combined and personalized with adult assets. All composite assets must be approved by the *All of Us* Division of Communications prior to use. An approval process with pediatric asset review guidelines will be agreed upon by the *All of Us* Division of Communications and the IRB and made available to sites who recruit pediatric participants. In addition, pediatric communications will be specifically assessed for whether the communication should be provided to the parents/legal guardians, to the pediatric participants (using age-appropriate content), and/or both. Review policies for content addressing parents/legal guardians versus pediatric participants may differ.

3.2 Outreach to HPO Members

The current program enlists HPOs (including regional medical centers, Veterans Affairs (VA) medical centers, and FQHC sites) as one method for enrollment of participants. Consistent with the Core Protocol, pediatric participants will be enrolled using the HPO model (see Section 1.3 for enrollment plans of each phase). Consistent with the current program, HPOs may use both nationally and locally developed outreach approaches to engage eligible individuals and families in their catchment area. HPOs can use approved program advertising materials and/or locally developed outreach materials that go through an approval process. Advertisements include local program contact information. All locally developed outreach approaches and materials are created in collaboration with the Division of Communications and presented to the IRB as part of the Institution-Specific IRB Application (ISIA) process. HPO awardees must affirm they will not add non-HPO members who enroll in *All of Us* through their sites to the HPO's general operations marketing or advertising lists, and they will not actively recruit non-HPO members to join the HPO health system.

3.2.1 Outreach in Inpatient and High Acuity Settings

In light of the many factors impacting the ability to achieve informed consent, permission, and assent (as appropriate by age), special precautions are required around outreach for participation in the program in certain health care settings and scenarios. Decisional abilities of both the pediatric participant and their parent(s)/legal guardian(s) may be impacted by high acuity care (e.g., emergency or critical care) or by the inpatient medical experience, and there may be perceived pressure to enroll in the program from health care professionals. Due to these and a number of other factors, individuals in inpatient or other high acuity settings can be considered at greater risk of coercion, regardless of the recruiter's intention. To satisfy the requirements of 45 CFR 46.116, steps will be taken to minimize the potential for coercion or undue influence, either perceived or real. HPOs who wish to engage prospective pediatric participants in an inpatient or emergency care setting must take precautions to ensure:

- Patient safety
- Fitness, ability, and willingness of the parent(s)/legal guardian(s) to provide permission
- Fitness, ability, and willingness of the pediatric participant to provide assent, as appropriate
- Physical and emotional comfort of the pediatric participant and parent(s)/legal guardian(s)

Any outreach to enroll pediatric participants in inpatient, emergency department, or other high acuity health care settings must be consistent with the current program procedures and guidance and presented to the IRB as part of the ISIA process.

3.3 Outreach to Self-Directed Individuals

The Participant Center (TPC) develops strategies to engage individuals who are not in close proximity to physical *All of Us* locations and can enroll in a self-guided fashion. TPC's approach is designed to enroll individuals across the country and focus on UBR populations and those in areas not serviced by HPO awardees. TPC may also have a presence in HPO-covered regions to provide additional support for program outreach and clinic visits (see Section 1.3 for enrollment plans of each phase). Outreach materials may be developed for use by the TPC for engagement of families and older children, and eventually (in later phases) to support pediatric participation in a self-guided fashion. These outreach materials will require IRB review in a future amendment and go through a review process determined by the *All of Us* Division of Communications and the IRB.

3.4 Engagement with Communities

As demonstrated by the ongoing efforts of the *All of Us* Research Program, engagement with stakeholders, grassroots community organizations, and researchers are foundational to the program. Active participation of these communities is foundational to the program's pediatric efforts as well, ensuring engagement with pediatric participants across the lifespan.

A national network of partners has been established and will continue evolving which will help initiate and facilitate the four essential and unique components of the creation of an active

participant community: outreach, engagement, recruitment, and retention. *All of Us* defines outreach as unidirectional interaction, such as providing materials and information to an audience; engagement as a broad range of relationship-building bidirectional interactions, including information sharing, consultation, collaboration in decision making, and empowered action between the program, people, awardees, and other partners; recruitment as facilitating enrollment in the program; and retention as ongoing activities with pediatric participants after enrollment.

The national, state, and local engagement partners are building a national network of trusted leaders by raising awareness about the program among African Americans, Asian Americans, Native Hawaiians and Pacific Islanders, Hispanics and Latinos, LGBTQ+ communities, disability communities, rural populations, and older adults in an effort to complement and enhance the program's existing outreach and recruitment efforts. Several of these awardees also engage diverse communities of researchers to use the *All of Us* data resources to advance precision medicine and motivate diverse communities to join *All of Us*. Also see Section 4.7.3 Considerations for American Indian/Alaska Native Individuals.

To date, the program has several national engagement and engagement innovator partners with over 115 additional community partners to support outreach efforts, many of whom have specific outreach to children and/or families. These include, but are not limited to, partners such as American Association on Health and Disability, Stanford/PRIDEnet, National Alliance for Hispanic Health, and University of Utah. Further post-enrollment engagement activities are described in Section 11.

3.5 Mobile Engagement Asset (MEA)

As additional outreach, the *All of Us* Research Program has deployed mobile engagement assets (MEAs) to bring awareness about the program to UBR populations. MEA strategies will be consistent with the current Core Protocol, and any MEA materials describing pediatric participation in *All of Us* will require IRB review in a future amendment.

3.6 Accessibility of Outreach and Enrollment Materials

Consistent with current program procedures and 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, participant-facing materials are currently written at a 7th grade reading level or lower. Target readability metrics for materials directed towards parents/legal guardians will be consistent with those specified by the Core Protocol. In addition, outreach and enrollment materials that are intended to be viewed by the pediatric participant in the 7–12 years and 13 years to age of majority age groups will be calibrated to the youngest end of each age group.

Section 4: Enrollment

Enrollment in the *All of Us* Research Program is voluntary.

4.1 Enrollment Strategies

All enrollment approaches currently employed by *All of Us* awardees can be utilized to promote pediatric enrollment, provided IRB-approved content is utilized.

4.2 Pediatric Account Creation

Account management for pediatric participation will incorporate technical enhancements that address issues such as privacy, family relationships, account linkages between parent(s)/legal guardian(s) and pediatric participant (i.e., what constitutes a "family" account), associated account access privileges and roles, and rules governing creating, modifying, viewing, or withdrawing pediatric participant records. One intent of account linkages is to enable researchers to review family-level (e.g., parent-child relationships) data and individual data within the *All of Us* cohort, inclusive of adult and pediatric participants. Account management will also include development of a transparent, predictable, and dynamic process of account management that enables appropriate privacy of, and access to, return of data when a pediatric participant reaches adolescence, and again as they transition into adulthood.

The program expects to offer several opportunities for pediatric participants and/or their parents/legal guardians to create accounts, each contingent upon the specific age group of enrollment. These processes will include being able to create a sub-account within the parent's/legal guardian's account using parent/legal guardian facilitation and enabling independent login to the Participant Portal (Core Protocol Section 11.3.1) for pediatric participants when they reach specific age criteria. Based on program-determined eligibility criteria, the system will allow new permission/assent and data collection opportunities (such as new surveys) to be offered within child accounts of already existing adult accounts. This account information is stored securely in the Participant Portal host database. Once the pediatric participant and their parent(s)/legal guardian(s) complete permission/assent, a copy of this information is also transferred to the Raw Data Repository (RDR). The RDR is described in depth in Core Protocol Section 14: Creation of the *All of Us* Research Program Resources.

The participant's account information is used to offer local support and assistance to those who have created an account (including support directly to pediatric participants in later phases). The account information is also available to a select number of trained staff for data validation and regulatory purposes. The DRC generates a unique internal Participant ID (PID), represented as a random 10-character string (format P000000000) that is used to access participant information without using explicit personal identifiers.

An *All of Us* account is created electronically for each pediatric participant. Mitigations of potential access barriers for account creation are proposed to support participation and allow for diversity and inclusion within communities. Trained staff, Computer Assisted Telephone Interviewing (CATI, Appendix C14) staff, or the Support Center (Appendix W) facilitate this process and accommodate individuals with differing levels of technological capability. Upon participant request, trained staff may provide assistance by creating log-in and/or password

information with participants. This may include helping participants to meet the technical requirements of the password creation. Staff will not record log-in or password details.

4.3 Information Collected to Render Localized Permission/Assent

Following account creation, persons wishing to enroll a pediatric participant in the program need to provide information on the following:

- Language preferences of the parent/legal guardian and the child (English or Spanish).
- Attestation that the respondent is either a parent or a legal guardian of the child being enrolled.
- Affirmation that the respondent is of legal age (i.e., a legal adult) in their state of residence.
- Confirmation of the pediatric participant's date of birth.
- Provision of 1) the state of residence of the pediatric participant and 2) the state where the pediatric participant receives most of their health care. This enables compliance with state-specific requirements, such as disclosure of the California Experimental Bill of Rights (Appendix F3) to individuals participating in California.
- Identification of whether the pediatric participant receives health care at any of the program's affiliates within the 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.

4.4 Permission/Assent Processes

Informed consent is fundamental to the ethical practice of human subjects research. Disclosure, willingness (i.e., voluntariness), and decisional capacity make up the core of valid informed consent processes. All persons wishing to participate in *All of Us* complete an informed consent process (Appendix E and F series) and receive access to a copy of the permission and assent forms for their records. Participation of an individual under the age of majority requires permission from one parent/legal guardian. In addition, when appropriate by age (i.e., 7 years of age and older) or by transitioning to an older age group with the program, assent of the pediatric participant is also required. These two elements are hereafter referred to as "permission/assent."

4.4.1 Permission Process

The permission process is administered and documented electronically. It is designed as an interactive, modular process, with just-in-time information and opportunities for periodic updates. The electronic permission process is self-paced, and there is no time limit to complete it. Paper printouts are available at HPO sites participating in pediatric enrollment for review if needed. Individuals can navigate, repeat, pause, and review according to their own information needs. The permission process can be experienced as a self-navigated, supported, or hybrid process. Individuals can choose their preferred permission experience. Individuals can navigate the permission process through the Web or mobile *All of Us* application, either alone or with the assistance of another person. Individuals can also request support from trained HPO site staff.

Permission materials are available in English and Spanish. Translated materials are generated through an IRB-approved translation procedure (Appendix P) and provided to the IRB for their records. Verbal interpretation into other languages without the provision of IRB-approved written translation of the information is not allowed.

Site-specific changes to the permission form or process (ePermission screens or longform version) are not allowed under any circumstances.

When enrolling a neonate, the permission process must occur with the parent(s)/legal guardian(s) after the child has been born.

4.4.2 Assent Process and Dissent

A description of the assent process will be provided to the IRB in a future amendment for each phase (age range) of the research. The assent process will include a developmentally appropriate and age-specific overview of program activities for those 7–12 years of age, and for those 13 years of age to the age of majority. The program will not seek assent of children under the age of 7, but children will be told in age-appropriate ways what will happen and why.

Assent materials will be available in English and Spanish. Translated materials are generated through an IRB-approved translation procedure (Appendix P) and provided to the IRB for their records. Verbal interpretation into other languages by consortium staff without the provision of IRB-approved written translation of the information is not allowed.

Site-specific changes to the assent forms or process (eAssent screens or longform version) are not allowed under any circumstances.

In cases of active dissent, program staff will acknowledge and act in accordance with the child's wishes. Site staff make decisions whether to proceed with research procedures by using professional experience to determine if the behavior is active dissent (i.e., more than expected reluctance/anxiety related to the procedure). Site staff also involve the parent(s)/legal guardian(s), soliciting their judgment regarding dissent to supplement their own professional judgment, and assistance for providing reassurance to the child to potentially proceed with research procedures. Study teams will follow the ethical principles outlined by Brown et al. to recognize, address, and respect dissent in pediatric participants, including provision of age-appropriate information and activities, ongoing monitoring and addressing of distress (with parent/legal guardian involvement), and respect for the parent/legal guardian as the decision maker (without coercion or undue influence).[14]

4.4.3 Considerations for On-Site Enrollment

Parents/legal guardians of pediatric participants who enroll at an HPO site are 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 permission/assent and audiovisual content.

The parent/legal guardian is clearly informed that their decision regarding the participation of a child in the program does not impact the care the child receives (nor care the parent/legal guardian receives).

4.4.4 Additional Modalities of Permission/Assent

To ensure the accessibility, inclusivity, and diversity of the program, the electronic permission/assent process is adapted to meet the presentation needs of children and people with variable learning styles and health literacy levels. For permissions and authorizations, materials will be written at a grade 5 reading level. Key concepts will be presented in "bite-sized" chunks via eScreens. Videos will also be used in some permissions to help break up reading the content, and to present specific key or complex topics through multiple modalities. Links to additional information (e.g., Learning Center) will be used strategically to cover topics adult participants have previously had the most questions about. Formative evaluation questions will follow eScreen content and precede the long form agreement. They will serve to reinforce key concepts and alleviate common misunderstandings. Plans for assent materials are ongoing but will be presented at an age-appropriate level and developed in consultation with subject matter experts. These additional modalities of permission/assent do not preclude person-to-person contact for questions or concerns. Trained staff are available to address questions or concerns about the program.

Regardless of the approach to permission/assent, the pediatric participant and their parent(s)/legal guardian(s) receive electronic access to a copy of the permission and assent forms for their records.

4.4.5 Supported Permission/Assent

As previously described, the permission/assent process may be self-navigated or completed with support. There are circumstances where individuals intellectually capable of providing permission/assent may require or prefer assistance with the process due to physical, social, educational, or other limitations. For example, facilitated permission/assent is offered to persons who are visually impaired or unfamiliar with electronic technology. Trained site staff experienced in facilitating permission/assent procedures are available to facilitate *All of Us* consent procedures. They utilize approved electronic permission/assent visual aids and text and engage the prospective pediatric participant and/or their parent(s)/legal guardian(s) in a discussion of permission/assent to answer any additional questions or concerns. Trained site staff who facilitate the permission/assent process are required to co-sign the permission and/or assent documents.

4.4.6 Provisions for Serial Assent and Permission

The *All of Us* Research Program anticipates that pediatric participants may remain participants in the program as they cross age thresholds associated with requirements for permission/assent, re-permission/re-assent, and consent at age of majority. Specifically, when reaching age 7 years and 13 years, assent with the age-appropriate documentation will be required to support ongoing active participation (i.e., no active participation of the pediatric participant such as PPI or PM&B will be allowed without (re)permission and (re)assent). However, passive secondary data collection (e.g., EHR data) will continue until either permission/authorization is withdrawn (as applicable), participation is withdrawn, or the child reaches the age of majority. The pediatric participant's account will remain active, unless participation is withdrawn, enabling the program to request permission/assent.

The program will reach out to the pediatric participant through their parent(s)/legal guardian(s) to request permission/assent for any new or different procedures that are part of participation for the child's new age group. When completed, the new permission/assent documents will be provided via the child's *All of Us* account to the pediatric participant and their parent(s)/legal guardian(s) for their records. They may also choose to have the PDF of the permissions/assents emailed to them upon completion and anytime thereafter. A description of the timing and process for requesting permission and assent at ages 7 and 13 years will be provided to the IRB in a future amendment. Further, for the scenario of pediatric participants reaching the age of majority, a future amendment will request from the IRB for any necessary waivers of consent and detail the process for requesting consent from the now-adult participants.

4.4.7 Provisions for Redocumentation of Permission/Assent

While enrolling pediatric participants, it may be necessary to re-document permission/assent if it is found that an individual was presented with or completed incorrect permission or assent form(s). Given centralized procedures for obtaining and documenting permission/assent, this is expected to be unlikely to occur. Still, the program has an IRB-approved approach (Appendix E10) to facilitate redocumentation of adult consent and, if needed, we will update this approach to include content for permission/assent.

4.5 Electronic Permission/Assent Documents

Using an electronic permission/assent process throughout the program ensures consistency of the permission/assent information. The electronic permission/assent process includes information on the detailed nature, purpose, procedures, benefits, and risks of and alternatives to participating in the *All of Us* Research Program.

Parents/legal guardians may be required to sign additional documents (e.g., the California Experimental Subject's Bill of Rights [Appendix F3]), as mandated by state law.

Due to the longitudinal nature of the study and the patchwork of state regulations regarding research—and to provide a flexible pediatric participant experience—the *All of Us* permission/assent is modular. Each permission module requires an electronic signature from one parent/legal guardian. When appropriate by age and cognitive ability, each assent module requires indication of assent of the pediatric participant:

1. **Permission to Participate (Appendices EP1 & FP1):** The permission module gives an overview of all program activities, including the current status of the potential for return of DNA results for pediatric participants. Signing the permission form indicates general understanding of the program and approval to take part in the PPI, data linkage, PM&B collection, biobanking, biomarker assays, genomic analysis, and sensor/wearable technology activities if invited. For all ages, pediatric enrollment requires completion of the permission to participate by one parent/legal guardian.

   This module contains ePermission screens that present key concepts through a mix of short videos and concise text blocks. The screens are followed by a set of formative evaluation questions designed to help reinforce key concepts and alleviate common misunderstandings. Parents/legal guardians are then presented with the longform Permission form that reviews all elements of their child's participation in the program for

the age range at hand (i.e., birth to 6 years old, 7–12 years old, or 13 years old to majority). The longform is written at grade 5 reading level to be understandable to an audience with a wide range of literacy levels. Callout boxes are interspersed throughout the form to remind parents/legal guardians of key information or to highlight information that has caused concern or confusion in the adult informed consent process for the program.

Pending IRB determination that this protocol falls under "research not involving greater than minimal risk" (45CFR46.404; 21CFR50.51) or "research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects," (45CFR46.405; 21CFR50.52) permission will be required from a minimum of one parent/legal guardian to enroll their child (45CFR46.408; 21CFR50.55).

In the event that a child has parents with joint custody (distinct from co-guardianship as discussed in next paragraph) and one parent is known to disagree or if the program learns at any time that a parent opposes enrollment of their child in the program (i.e., if another parent/legal guardian notifies the program), the program will not enroll the child (also see Section 8 about withdrawal). However, if the parent providing permission has sole legal responsibility for the care and custody of the child, the program will proceed with enrolling the child.

Permission from only one legal guardian of the child will be required for enrollment. The permission form includes a statement that the parent/legal guardian signing has the authority to give permission for the child to join the *All of Us* Research Program and if they are required to make decisions about the child in agreement with another parent or legal guardian, such as in the case of co-guardianship, they have done so prior to signing this form. Local HPO partners will provide guidelines in their ISIA for abiding by institutional policies and applicable local laws relevant to obtaining guardian permission.

2. **Assent to Participate (Appendix TBD)**: The pediatric participant assent module will provide an age-appropriate and age-specific overview of program activities for those 7–12 years of age, and for those 13 years of age to the age of majority. No assent module will be provided to pediatric participants under age 7 years. Completion of the assent module followed by indication of assent by the pediatric participant indicates general understanding of the program and approval to take part in the PPI, data linkage, PM&B collection, biobanking, biomarker assays, genomic analysis, and sensor/wearable technology activities if invited. For ages 7 years and older, pediatric enrollment requires both completion of the pediatric participant assent module by the pediatric participant and indication of assent by the pediatric participant. A description of the methods for indicating assent will be provided to the IRB in a future amendment.
3. **HIPAA Authorization for Research EHR/Part 2 Supplement (Appendices E$_P$2 & F2):** This module gives details about allowing the program to request and receive a pediatric participant's EHR, including health records protected by 42 CFR Part 2 (drug and alcohol abuse patient records), referred to as "Part 2" records. Parents/legal guardians will review eAuthorization screens that present key concepts about sharing their child's EHRs with the program through concise text blocks. The screens are followed by a set of formative evaluation questions designed to help reinforce key concepts and alleviate common misunderstandings. All messaging in the eAuthorization screens is tailored to

pediatric participation. However, the longform authorization is a universal form that can be utilized by an individual authorizing release of their own records, by a parent or legal guardian authorizing release of their minor child's records, or by a legally authorized representative authorizing the records of the adult they represent. This is in line with standard practice for HIPAA authorization forms and will reduce the number of population-specific forms the program must accurately keep up-to-date and displayed.

State-specific versions of the authorization form will be used as needed to meet state laws and regulations regarding the release and use of health record data. For all ages, the parent(s)/legal guardian(s) will be offered the opportunity to provide this authorization for program access to EHR data. They are not required to sign the authorization form for the pediatric participant to be enrolled into the program; EHR data will only be acquired by the program if the parent(s)/legal guardian(s) provides permission by completing the authorization module and form. Consistent with the Core Protocol, EHR authorization is required to be eligible for the pediatric participant to provide a biospecimen. The parent's/legal guardian's authorization will remain in effect until the parent/legal guardian withdraws authorization or until the pediatric participant reaches the age of majority.

4. **Permission for Return of DNA Results (Anticipated for Future in Appendices E$_P$3 & F$_P$2)**: This module will explain the potential risks and benefits of receiving genetic results about the pediatric participant from the program and will obtain permission to perform genetic testing on an individual for the purpose of return of results and permission for return of those DNA results. DNA results generated for the purpose of returning results to participants (i.e., Results Reports) will only be generated and returned to the pediatric participant and/or their parent/legal guardian by the program if the parent/legal guardian provides permission. A future amendment to this protocol will provide these appendices, together with relevant appendices describing the return of DNA results processes (Appendix Q series). The Permission for Return of DNA Results module will only be provided to parents/legal guardians after IRB approval and FDA IDE clearance has been obtained to allow the *All of Us* Research Program to provide DNA results to pediatric participants. Until such approvals are in place, the Permission to Participate, described above, will include statements that (1) at this time, return of DNA results to pediatric participants is not available; (2) work is ongoing to make this available in the future, but return of DNA results cannot be guaranteed for pediatric participants; and (3) if return of DNA results to pediatric participants becomes possible in the future, the parent/guardian will be asked to provide permission before generation or return of these results. This approach is transparent, aligns with regulatory requirements, and supports *All of Us* Research Program Core Values.

5. **Assent for Return of DNA Results (Anticipated for Future, Appendix TBD)**: This module will explain to the pediatric participant what genetic testing is and the potential risks and benefits from receiving genetic results from the program at an age-appropriate level. The age at which the program will require assent for return of DNA results is still being determined in consultation with subject matter experts. A future update to this protocol will be made when this has been determined. No assent module will be provided to pediatric participants under age 7 years (Phase 1). For pediatric participants of the ages where the program requires assent for return of DNA results, DNA results reports will

only be generated (for the purpose of returning results) and returned to the pediatric participant and/or parent/legal guardian by the program if the pediatric participant provides assent.

4.6 Data Oversight and Choice of Law

Consistent with the current *All of Us* Research Program, there are a considerable number of distinct state laws and regulations governing the collection and use of various data types collected by the program. The *All of Us* Research Program obtains guidance from the NIH Office of the General Counsel and the Office for Civil Rights, which provide recommendations on the appropriate application of state regulation in the context of this national research program. The program uses this guidance in revisions of pediatric participant materials, permission/assent, and workflow for all submissions, including the pediatric supplemental protocol.

4.7 Special Considerations for Enrollment

Because the *All of Us* Research Program intends to be a research program that is inclusive and reflects the diversity of the U.S., regardless of their demographic or socioeconomic statuses, some populations merit special consideration.

The vulnerable populations that are excluded or included in the initial enrollment efforts are summarized in Table 4-1: Vulnerable Populations Excluded or Included at Launch. Separate protocol amendments may be developed and submitted to the IRB that include plans to enroll vulnerable pediatric participants who are excluded at this time, such as wards of the state, and emancipated minors.

Table 4-1: Vulnerable Populations Excluded or Included at Launch

Vulnerable Population	Status at Launch
Emancipated minors	Excluded
Minors who are incarcerated	Excluded
Wards of the state	Excluded
Neonates of uncertain viability and nonviable neonates	Excluded
Children with cognitive disabilities or delays	Included

4.7.1 Considerations for Pediatric Participant and Family Compensation

Consistent with the Core Protocol, the program provides monetary compensation to a single accompanying adult upon completion of a PM&B visit. The purpose of this compensation is to acknowledge and express gratitude for their contributions of time and travel related to their child's participation. Additional parents/legal guardians or adults who also attend the PM&B visit will not receive compensation. The accompanying adult does not have to be an *All of Us* participant to receive compensation (e.g., if one parent provides permission for their child to join, but another parent or a grandparent brings the child to the scheduled PM&B appointment).

The accompanying adult is paid according to the amount, timing, frequency, and method as outlined in the Core Protocol. This means an accompanying adult could potentially be

compensated multiple times—once for each pediatric participant they accompany to a PM&B visit, independent of any compensation to the adult for their own participation.

Pediatric participants of all ages receive an age-appropriate, non-monetary, functional token of appreciation at each in-person study visit. The tokens are culturally and developmentally appropriate and of minimal promotional value so as not to create undue influence to participate (e.g., toys, books, blankets, towels, T-shirts, etc.). This compensation serves as an age-appropriate recognition of the time and effort of participation.

A monetary compensation strategy for pediatric participants ages 13 years to age of majority will be developed and submitted to the IRB in a future amendment.

Payment information and distribution of tokens of appreciation are recorded by sites in a secure spreadsheet. In addition, families may be eligible for reimbursement of transportation or parking costs, depending on the site-specific business practices of their enrollment location and may also be eligible for additional compensation (monetary and non-monetary) as part of site-specific recruitment, engagement, and retention practices (subject to IRB approval as part of a site's ISIA). If a pediatric participant or their parent(s)/legal guardian(s) withdraws their participation, they are not expected to return any previously paid monetary compensation or tokens of appreciation, nor will the parent/legal guardian receive additional monetary compensation if the pediatric participant rejoins the program.

4.7.2 Compensation for Injury

No serious injuries are anticipated as a result of a child participating in the *All of Us* Research Program. However, if a pediatric participant is injured as a direct cause of their involvement in the *All of Us* Research Program, Core Protocol Section 10.1.3 will be followed for the provision and compensation for care of injuries that were a direct cause of participation in the program.

4.7.3 Considerations for American Indian/Alaska Native Individuals

The *All of Us* Research Program is committed to working with Tribal Nations to respectfully address issues related to research involving American Indian and Alaska Native (AI/AN) children. Pediatric enrollment and participation in the *All of Us* Research Program may include individuals who self-identify as AI/AN. Pediatric enrollment and participation of AI/AN children in the program will adhere to the same program policies and restrictions as established for AI/AN adults as described in the current Core Protocol. For example, information on Tribal affiliation (if collected) will not be made available to researchers unless there is an agreement with a specific Tribe. The program will utilize experts in AI/AN pediatric health research and from AI/AN groups and Tribal nations to develop guidance for AI/AN children and their families. The program will not undertake focused outreach to tribal communities until after this guidance is developed, but individuals who self-identify as AI/AN are still eligible to enroll. Any critical events that require consultation with Tribes will be addressed in alignment with the NIH and Health and Human Services (HHS) Tribal Consultation policies.

4.7.4 Considerations for Emancipated Minors

At this time, we will not enroll emancipated minors in the *All of Us* Research Program. The legal criteria to be deemed an emancipated minor is determined by the relevant jurisdiction. The

complexity of, and variation between, state laws impose significant operational challenges to verify one's emancipated status. To ensure we do not erroneously permit minors to consent to participation for themselves in violation of local age of majority laws (and therefore federal research regulations), such minors will not be able to participate in the early phases of this protocol. If we learn that a pediatric participant has become emancipated, we will "deactivate" (suspend active participation but authorize continued use of data and biospecimens; parent-/former legal guardian-/participant-facing term "pause") their participation until such a time as we are equipped to allow for participation by emancipated minors or until they reach the age of majority.

4.7.5 Considerations for Incarcerated Minors

Consistent with the Core Protocol for the *All of Us* Research Program, we will not enroll minors who are incarcerated. Some pediatric participants may become incarcerated over the course of their participation in the *All of Us* Research Program. If we learn that a pediatric participant has become incarcerated, we will "deactivate" (suspend active participation but authorize continued use of data and biospecimens; participant-facing term "pause") their participation until such a time as we are equipped to allow for participation by incarcerated minors or until they are no longer incarcerated. At either of these points, "reactivation" of their participation would be contingent upon renewed permission/assent, as appropriate.

4.7.6 Considerations for Wards of the State

At this time, we will not enroll minors who are wards of the state. Minor wards have diminished parental protections and are deemed an especially vulnerable population of pediatric participants. Additional program protections are needed to ensure wards of the state are not enrolled in research studies without clear justification and careful consideration of their individual interests to mitigate any risk of coercion.[15]

Pediatric participants may become wards of the state over the course of their participation in the *All of Us* Research Program. If we learn that a pediatric participant has become a ward of the state, we will "deactivate" (suspend active participation but authorize continued use of data and biospecimens; parent-/ legal guardian-/participant-facing term "pause") their participation, until such a time as we are equipped to allow for participation by minor wards of the state or until they are no longer a ward. At either of these points, "reactivation" of their participation would be contingent upon renewed permission/assent, as appropriate.

4.7.7 Considerations for Children of Minor Parents

At this time, every pediatric participant must have at least one parent/legal guardian who is at or above the age of majority in order to be enrolled (see Section 1.3.3). State laws and rulings imply that the minor-mother or minor-parents, depending on locale and circumstances, have custodial and parental rights over the child. That creates an unusual circumstance where, when a child of a minor-parent is to be enrolled, the minor-parent will give parental permission for their child's participation. However, for the minor-parent's own participation in *All of Us*, they would assent and the minor-parent's parent/legal guardian would provide permission.

In addition to these complex permission/assent dynamics, additional support around the consent/permission/assent and enrollment process may be warranted to ensure the minor-parent is making a fully informed decision and is not subject to any undue coercion. We will use the intervening time before later phases to consult with relevant subject matter experts and other stakeholders, as well as conduct additional research in this area. This will allow us to ensure any protocol for enrolling children of minor-parents abides by applicable laws and regulations and integrates ethical and psychosocial considerations for such enrollment.

4.7.8 Considerations for Children with Cognitive Disabilities

Children with cognitive disabilities or delays may be enrolled, with permission from their parent(s)/ legal guardian(s). For children enrolled at a very early age, such as in the first year of life, enrollment may precede any manifestation or diagnosis of developmental delay or disability. Including these individuals is consistent with the values of the program and will enable scientific insights to improve the health trajectories of future children with developmental differences.

Just as inclusion of pediatric participants in *All of Us* aligns with the program's Core Values #1 "Participation is open to all" and #2 "Participants reflect the rich diversity of the United States," so too does inclusion of children with cognitive disabilities. Moreover, inclusion of children with cognitive disabilities further enables precision medicine research to benefit all children, rather than only some. As a longitudinal research program beginning with enrollment of children from birth to age four, we anticipate some pediatric participants who experience cognitive delays or disabilities subsequent to enrollment. Therefore, we are intentionally planning on inclusion of such pediatric populations.

Provisions for continued participation and enrollment of children with cognitive disabilities who are age 7 years and older (who may be unable to participate in assent activities designed for typically developing children and adolescents) will be provided in a future amendment. Indications of active dissent from the potential participant will be honored and they will not be enrolled (see Section 4.4.2). Provisions for obtaining consent once children with cognitive disabilities reach the age of majority will be outlined in the Core Protocol.

Section 5: What Is Involved? Program Procedures

Once a pediatric participant and their parent(s)/legal guardian(s) have confirmed their decision to join the *All of Us* Research Program by completing the permission/assent process, the pediatric participant is eligible to start contributing information to the program.

To ensure the person providing the electronic signature(s) on the permission and authorization forms is who they assert they are, trained staff must follow site-specific policies and procedures to confirm the signatory's (in this case, the parent(s)/legal guardian(s) of the pediatric participant) identity at the beginning of their appointment to contribute biospecimens. The site-specific policies and procedures must meet, but may exceed, the minimum requirements set by the *All of Us* "Minimum Participant ID Verification Requirements for Physical Measurement and Biospecimen Appointments" policy. Site staff must also confirm that the potential pediatric participant wishes to move forward with procedures listed in the permission/assent documentation. The process for confirming identity at each site is defined in the site-specific ISIAs. The program may also employ digital ID verification procedures that meet or surpass the

standards set by the policy. This is required in cases where the program allows pediatric participants to donate specimens remotely or to allow someone other than the signatory parent/legal guardian to accompany the child to a biospecimen collection appointment.

The amount of time to complete pediatric participant enrollment in one sitting may range between one to three hours (excluding time required for permission/assent). Some pediatric participants may complete certain modules ahead of time; therefore, the time required in one sitting may be significantly less than two hours. These times are not intended to reflect time for transportation to the site or wait times prior to initiation of data collection.

5.1 Participant-Provided Information (PPI)

In addition to contact information and data for creating an account, the program collects extensive information about a pediatric participant's health status through self-completed surveys (incorporated into the Core Protocol as Appendix G series). This PPI includes data relevant and necessary for scientific research studies (e.g., personal and family medical history, socioeconomic factors, and health care access and utilization). For the pediatric participants age 12 years and under, all information will be provided by a parent/legal guardian (on behalf of the child). For pediatric participants age 13 years to age of majority, some information will be provided by the pediatric participants, and some by parents/legal guardians.

Most questions are selected, or modified, from various health-focused surveys previously validated in large cohorts and cross-sectional studies: 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, Environmental Influences on Child Health Outcomes (ECHO], the National Children's Study (NCS), the National Survey of Children's Health (NSCH), Centers for Disease Control Q-Bank Tool, PhenX (Phenotypes and eXposures) Toolkit, and other similar surveys.

The PPI modules used with pediatric participants are developed in English by the PPI Committee and expert task forces for each prioritized content area. Content is designated regarding who is expected to provide the information, based on the content and the age of the pediatric participant (i.e., the parent/legal guardian; the parent/legal guardian with input from the pediatric participant; the pediatric participant with assistance from parent/legal guardian; and/or the pediatric participant). The questions are further refined through testing using standard cognitive interviews and online user assessment based on a need for testing identified by the PPI Committee and expert task force. This testing 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 pediatric participants. Consistent with the guiding principles and ongoing practices of the program, each PPI survey will be assessed for readability as described in Core Protocol section 6.1.1, revised to improve clarity, and re-reviewed to ensure retention of essential meanings and concepts. The IRB-approved English-language versions of survey modules are translated in other languages, using the IRB-approved translation procedure (Appendix P). All Spanish translated modules are tested in Spanish.

There are currently three surveys available for parents/legal guardians of pediatric participants to complete at enrollment: The Basics (Appendix G_P1), Overall Health (Appendix G_P2), and Environmental Exposures (Appendix G_P3). Individuals will be invited to complete additional

surveys as they become available. Survey respondents can save their answers and return to complete each survey later if needed. For survey respondents who may need more assistance to complete surveys, Computer Assisted Telephone Interviewing (CATI) is available. CATI is a telephone surveying technique in which surveys are completed by a CATI interviewer over the telephone (Appendix C14).

Pediatric participants and/or their parent(s)/legal guardian(s) will be invited to complete additional surveys about the pediatric participant's health throughout the duration of their participation. Additional surveys in domains such as diet, physical activity, medications, and sleep may be developed on an ongoing basis. New surveys will be submitted to the IRB for review and approval prior to implementation.

Pediatric participants and parents/legal guardians 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 and/or the Support Center (Appendix W). Pediatric participants and parents/legal guardians are also able to share their experience by completing IRB-approved structured surveys about the *All of Us* Research Program.

5.2 Physical Measurements

Pediatric participants have an option to have a standardized set of physical measurements collected and recorded in HealthPro (Core Protocol section 7.5.1). The baseline physical measurements include physiologic (e.g., blood pressure and heart rate) as well as anthropometric (e.g., height/length, weight, head and waist circumference) measurements; measurements requested by the program are age specific. See Appendix U1 for details on the eligibility criteria, collection, storage, and reporting of physical measurements in pediatric participants along with risks, benefits, access to physical measurement information and return of actionable health-related results. See Appendix U2 for communications related to physical measurements.

5.3 Biospecimen Collection

Pediatric participants have an option to have a standardized set of biospecimens collected including blood, urine, saliva, and/or buccal swabs. Donation of any biospecimen is optional, and not required for participation in the program.

While blood is the most reliable source of high-quality DNA for research, pediatric participants and/or parents/legal guardians may not be willing to provide blood or may only permit blood collection if the pediatric participant requires a blood draw for clinical reasons (e.g., routine screening or diagnostic assessment). See Appendix T1 for details on the eligibility, collection pathways, shipping, storing, and accessing biospecimens. See Appendix T2 for communications related to biospecimen collection.

Although some may advocate for saliva to replace blood for DNA collection in pediatric populations as a way to minimize risk, the scientific benefit of analyzing blood outweighs the risks of collecting this sample type. Saliva samples do not provide the consistent, high-quality volume of DNA that is needed for this research. Among adult participants, the program has observed a 12%–15% sample failure rate for saliva samples compared to a <5% failure rate for blood. The saliva failure rate is expected to be higher for pediatric participants. In order to maximize success in achieving the program's goal to generate a clinical grade whole genome

sequence on every participant who provides a sample, collection of blood is preferred. Beyond DNA analysis, assessment of additional biomarkers (e.g., from plasma), which are of particular interest for the pediatric population, will not be possible from saliva collection alone.

5.4 Electronic Health Records (EHRs)

Consistent with the current Core Protocol, parents/legal guardians of pediatric participants are asked to authorize linkage of the pediatric participant's EHR information, if available. The processes and procedures for EHR linkages will proceed as outlined in the Core Protocol. As pediatric participants reach the age(s) at which they can make autonomous decisions about consent and confidentiality for certain types of health care per the laws of their jurisdiction, the pediatric participant will begin to gain sole control over sharing those records with the program as well as revoking such sharing.

5.5 Data Linkage

Consistent with the current Core Protocol, the *All of Us* Research Program will link data collected or generated by the program with data from other sources. The data sources used by the Core Protocol will be used for pediatric participants, including the use of geolocation data linkage (e.g., using home address to develop a dataset of social, community, and environmental variables). We will leverage *All of Us* award mechanisms focused on data linkage to expand pediatric research utility.

An amendment will be filed with the IRB for the addition of any new data sources to the program's dataset. For example, there are additional linkages specific to young cohorts that may be informative. These include screening programs (e.g., State-run Newborn Screening, CDC National Childhood Blood Lead Surveillance Data); tracking programs (e.g., State-based birth defects tracking systems, Immunization Information Systems); survey data (e.g., National Youth Tobacco Survey, Pregnancy Risk Assessment Monitoring Systems); and other data types. EHR data might be provided from a child's medical provider (well visits, yearly checkups, sick visits) that is not associated with an HPO.

While the permission to participate encompasses data linkage, it is anticipated that prior to linking pediatric participant data with external sources, an amendment will be filed with the IRB for any linkages that require the DRC to share participant-identifying information to an outside entity. Some linkages may be accomplished in a privacy preserving manner rather than with PII, which might not require IRB review. Such IRB submissions would detail the data to be linked and the general methods for doing so. No additional permission/assent will be undertaken. The permission/assent forms discuss that identifying information may be shared in this process.

5.6 Early and Long-Term Pediatric Participant Involvement

5.6.1 Early Communication Workflow

For ages birth to 6, all communication will go to parents/legal guardians. In the future, we anticipate providing some information directly to children ages 7 and older (as well as their parents/legal guardians). Any communications intended to be viewed by the pediatric participants (in addition to *or* rather than parents/legal guardians) will be calibrated to the

appropriate age group. See Appendix JP3 for automated and manually generated messages to pediatric participants.

Contact mechanisms through the Participant Portal will enable communications in support of key protocol activities to be sent to the pediatric participant and their parent(s)/legal guardian(s). The Participant Portal delivers a message to the pediatric participant and their parent(s)/legal guardian(s) following successful permission and, if appropriate, assent. The transactional notification messages sent define the purpose and context associated with the protocol opportunities. The messages also welcome the pediatric participant and/or their parent(s)/legal guardian(s) to the program and provide information to facilitate awareness on how to progress through the program journey as a pediatric participant over time.

In contrast, if an individual has signed out without completing a started PPI module, a single message is sent indicating a session timeout. Reminders for users are sent out depending on the completion status of PPI modules.

5.6.2 Long-Term Communication

The *All of Us* Research Program is designed to allow and encourage pediatric participants to remain actively involved for decades. Following the collection of data at enrollment through PPI and PM&B, we will cultivate ongoing connection to pediatric participants and their parent(s)/legal guardian(s) through the two-way communication outreach strategies used in the current Core Protocol, as well as the pediatric-specific strategies listed below:

Opportunities to participate in:

- Updating contact information
- Additional surveys and other data sharing opportunities, as relevant
- Return of results-related activities
- Ancillary studies, as relevant
- Other avenues for participation as they arise and become approved program activities

Program updates:

- Inclusion of family-focused content in existing participant newsletters that include program milestones, new program features, enrollment numbers, events, or new findings
- Other national updates that correspond with program milestones or changes to the program, as needed
- Updates on research results originating from the program
- Local updates from the organization participants are paired with, or local updates relevant to their area from TPC

5.6.3 Communication Preferences

A central tenet of long-term involvement in the *All of Us* Research Program is that the participant controls both the frequency and method of communication from the program. Program

communications to pediatric participants (in future phases) and/or parents/legal guardians will be consistent with the current Core Protocol, including primarily electronic communication, with the option to choose email, SMS (Short Message/Messaging Service, i.e., text message), and/or in-app messages. The type of communication to the pediatric participant (in future phases) will be based upon the communication preferences selected in the pediatric participant's account.

5.6.4 Content and Review of Engagement Communications

All communications content for pediatric engagement efforts will be designed using program guidelines, strategies, and review processes set in collaboration with the Division of Communications, Research Compliance Branch, and the IRB. Communications review policies will be communicated to all partners during an onboarding process, as will any future changes. In addition, pediatric communications will be specifically assessed for whether the communication should be provided to the parent(s)/legal guardian(s), to the pediatric participant (using age-appropriate content), and/or both. Review policies for content addressing parent(s)/legal guardian(s) versus pediatric participants may differ.

Section 6: Participant Support

Consistent with the current Core Protocol, the pediatric participant journey can be experienced as a self-navigated, supported, or hybrid process. True to the program's Core Values and in recognition that individuals might require additional assistance throughout the participant journey, a number of resources are available. Program support is available from the Support Center (Appendix W1) and CATI (Appendix C14), trained staff, and the Genetic Counseling Resource (GCR) Call Center (Core Protocol Section 8.2).

Section 7: Risks and Benefits

There may be risks, discomforts, and inconveniences experienced by pediatric participants and/or parents/legal guardians as they participate in the *All of Us* Research Program. The risks and benefits outlined in the Core Protocol apply to pediatric participants as well as adults, and other potential risks and benefits specific to pediatric participation are described in Table 7-1.

Table 7-1: Research Activity Risk Level

Research Activity	Risk Level
Surveys	Minimal risk
Biospecimen collection	Minimal risk
Physical measurements	Minimal risk
EHR data linkage	Minimal risk
Other secondary data linkages	Minimal risk
Return of ancestry and traits DNA results	Not applicable to pediatrics
(Anticipated for Future) Return of health-related DNA results	(Anticipated for Future) Minor increase over minimal risk

7.1 Risks for Pediatric Participants and Risk Mitigation Approaches

7.1.1 Loss of Privacy/Confidentiality

Learning private or confidential information about a parent/legal guardian or family member may cause psychological, relational, or social harm for the participating child. Examples of such situations might be where the pediatric participant discovers something unexpected about a parent/legal guardian or the family unit from participating in this research including discoveries of non-parentage, adoption status, unexpected family health history, parent's/legal guardian's lifestyle, or habits (such as substance use), parent's/legal guardian's negative responses about the child, etc.

Similarly, the loss of the participating child's privacy or confidentiality due to their parents/legal guardians or other relatives learning information about them (e.g., parent/legal guardian viewing private information from electronic health records or survey responses) may also have psychological, relational, and social risks for the child. Examples of such situations could include exposing the child's gender identity, sexual orientation, mental health, behaviors, or activities the child engages in, attitudes towards parents/legal guardians, etc.

If the program decides to directly contact pediatric participants, there may be a greater risk of loss of privacy for pediatric participants than for adult participants because the pediatric participant may lack the resources or agency to be able to help protect their own privacy, particularly if they are only contactable through a third party. A pediatric participant may have a different living situation at the time of re-contact that could involve new persons becoming aware of the child's participation and personal information about the child.

The nature of the psychological, relational, and social risks that could result from the loss of privacy range from distress, loss of personal and/or group identity, disrupted family relationships or friendships, stigmatization, and more. The magnitude of these risks will vary depending upon the nature of the private information that is compromised, but the expected frequency is anticipated to be very low.

To minimize these risks, the program's confidentiality, privacy, and security protections are described in Core Protocol Section 16. See Section 4.2 of this protocol for information about pediatric account creation and mechanisms to protect privacy and confidentiality. The permission/assent processes, as well as ongoing education and contextualizing information in other communications, will help educate participants about ways to protect their own privacy.

The Children's Online Privacy Protection Act (COPPA, 16 CFR 312.3 "General requirements") does not apply to the *All of Us* Research Program because the program's website is not "a commercial Web site or online service" directed to children (16 CFR 312.2). However, to the extent possible, the program plans to voluntarily apply the online privacy protections COPPA offers to children under the age of 13 and their families to minimize risk through the following:

1. The program explains in the Privacy Notice on its website and in the parent/legal guardian permission form what information is collected from children, how it uses such information, and its disclosure practices for such information.
2. The program obtains verifiable parent/legal guardian permission prior to any collection, use, and/or disclosure of personal information from children.

3. The program will provide a reasonable means for a parent/legal guardian to review the personal information collected from their child (under the age of 13) and a mechanism to withdraw their child from the program, request their child's samples at the biobank be destroyed, and request their child's data not be included in future data releases to the Research Hub (see Section 10). (This point diverges from COPPA due to the program's data sharing model. However, these mechanisms aim to meet the spirit of the intention of this aspect of COPPA.)
4. The program does not condition a child's participation in the program or the receipt of compensation on the child disclosing more personal information than is reasonably necessary to participate in the research.
5. The program has established and maintains reasonable procedures to protect the confidentiality, security, and integrity of personal information collected from children (see Core Protocol Section 15.1 *All of Us* Data Access Governance).

7.1.2 Psychological and Social Risks

There are potential psychological and social risks, if a parent/legal guardian views responses while a pediatric participant completes a survey or after survey completion, particularly for topics that are of a sensitive nature (such as exposure to risky behaviors, substance use, mental health, eating disorders and others). A child's personal identity may not be acceptable within the family's culture or values, and parents/legal guardians may not be aware of the child's sexual/gender/religious/etc. identity. Some younger pediatric participants may complete surveys with their parent's/legal guardian's help or supervision, so the parent/legal guardian could see responses with sensitive information.

There is a potential that child abuse or neglect may be discovered by site staff or through survey responses. Site-specific reporting protocols will be used to inform the proper authorities.

Blood collection and physical measurement procedures can cause anxiety and fear in children, leading a child to actively dissent. Collection of biospecimens such as urine, saliva, and/or buccal swabs may cause mild embarrassment or discomfort if it is a new experience for the child. Adolescents may also experience discomfort or embarrassment if their parent/legal guardian is present during physical measurements or sees the results.

The magnitude of these risks will vary depending upon the individual child and their personal context, but the expected frequency is anticipated to be very low. To minimize these risks, the permission/assent processes, as well as ongoing education and contextualizing information in other communications, will help educate about possible risks.

During PM&B, the child, especially adolescents, will be offered as much choice as the program can provide about whether a parent/legal guardian is with them and who touches them to collect PM&B. Staff may offer options such as coming back another day, distractors (i.e., deep breathing, a video, game, music, conversation, etc.), or provide other ways to ease anxiety without forcing or coercing the child. For physical measurements, a parent/legal guardian may be allowed to assist with certain measurements, or staff might demonstrate unfamiliar equipment or have the child help in some way with the measurement. Pediatric participants may feel more comfortable self-reporting their own height and weight. If the pediatric participant continues to

actively dissent, the biospecimen or physical measurement will not be collected (see Section 4.4.2).

7.1.3 Physical Risks

The physical risks of biospecimen collection are the same for pediatric participants as for adults. There are no anticipated physical risks to the collection of saliva, buccal swabs, or urine. The upper limit for the amount of blood drawn from pediatric participants depends on the child's weight in order to minimize risk in infants and small children (Appendix T1). Staff will be trained and experienced with collecting samples from pediatric participants. There will also be a limited number of attempts to collect blood. The use of local anesthetic, ice, or a vibrating distractor (i.e., a Buzzy® device) will be left to the judgment of the phlebotomist. Blood draws will be timed with other clinical collections whenever possible to minimize physical pain and discomfort.

7.1.4 Return of Data and Results

There is a theoretical risk that as a result of the return of information, the pediatric participant may later regret knowing/learning something about themselves or their family. Children develop autonomy over time, and at the time of making a choice to view individual data or results, children are not able to know what kind of person they will grow up to be to make a true choice about what they really want to know or not know. There is no way to "un-know" something. In addition to decisional regret, this type of information also raises ethical concerns about a child's right to an open future.[16] It is the responsibility of the *All of Us* Research Program, the IRB, as well as the pediatric participant's parent/legal guardian to consider the potential benefit for return of information during childhood (e.g., to enable learning about science and health through discussion about genetics, or to learn about the child's health through review of study-collected data) versus the preservation of the child's future autonomy (e.g., to decide for themselves whether to receive information). This risk is minimized through the permission/assent processes, as well as ongoing education and contextualization of information in other communications, which will help educate pediatric participants and their parents/legal guardians about why they might or might not want to know information at this time.

There may be conflicts within the family over differing preferences and desires between parents/legal guardians and pediatric participants about what to know or not know. To minimize this risk, the language around the return of data or results will be carefully crafted to assist the parents/legal guardians and pediatric participants in considering the pros and cons of learning this information and to know what to do/not do after learning it. The program will also seek assent from children at appropriate ages for return of individual research results and will not return results when the pediatric participant has not provided assent in such instances.

Although there are no documented reports of this occurring, data or results may also be misinterpreted by the pediatric participant and/or their parent/legal guardian as medical diagnoses and could potentially lead to medicalization of some conditions, making harmful lifestyle changes (e.g., beginning a diet or exercise program if a child is considered overweight), or economic risks (e.g., pursuing costly and unnecessary treatments or preventative measures). To minimize this risk, data and results that are returned to pediatric participants and their parents/legal guardians will emphasize that the results are research results, and they should not

change the child's care without first consulting a medical professional. The permission/assent processes, as well as ongoing education and contextualization of information in other communications, will help educate about why they might or might not want to know information.

The physical measurements obtained from a pediatric participant may uncover an abnormal value that may be actionable, which would be managed according to Appendix U1. Pediatric participants and/or their parents/legal guardians may experience stress or anxiety as a direct result of receiving health findings or physical measurements that could be indicative of current or future illness or inconsistent with their understanding of their health status. As in the Core Protocol, a disclaimer will be included that the pediatric participant and/or their parent/legal guardian may wish to consult a health care provider to follow up on physical measurement information, and any questions about the impact of program-related information on personal health or clinical management should be directed to their health care provider. If a pediatric participant does not have a regular provider, the trained site staff will provide referrals upon request to appropriate organizations that work with underserved populations in their region. The pediatric participant and their family are responsible for the cost of any emergency services, follow-up clinical confirmation, or care through their health care provider.

7.1.5 Unknown Risks

Pediatric participants and/or their parents/legal guardians are informed in the permission/assent information that the research program may include risks that are currently unknown. When possible, the *All of Us* Research Program informs participants if new risks are identified that could affect their decision to participate.

7.2 Benefits

For pediatric participants and their parents/legal guardians taking part in the *All of Us* Research Program, the research is anticipated to offer the prospect of direct benefit to pediatric participants through access to information. Potential indirect benefits may stem from the opportunity to contribute to a large, diverse research dataset, learn about children's health and wellbeing topics, and interact with the program over time. Participant benefits are explained in Table 7-2.

Table 7-2: Participant Benefits

Potential Direct Benefits

Population	Potential Direct Benefits
All Pediatric Participants	• Access to the information about physical measurements, PPI responses, and other data in the participant portal • Access to genetic counselors (anticipated for future) • Chance for direct benefit from receiving information about DNA results that could be confirmed to be clinically actionable (anticipated for future)

Possible Anticipated Future Benefits

Pediatric Participants who have DNA Results Generated	Possible Future Actualized Direct Benefits
Uninformative Hereditary Disease Risk results	None, but there is still a chance for direct benefit in the future if a report is reissued with variant reclassifications
Positive Hereditary Disease Risk results	Results may be confirmed by health care provider to treat, prevent, or reduce the impact of disease
Medicine & Your DNA results	Results may be confirmed by health care provider to use in care
Ancestry and Traits results	Not applicable to pediatrics

Pediatric participants and/or their parents/legal guardians have access to their physical measurements and PPI responses via their Participant Portal. Additional data types that are available to pediatric participants, their parents/legal guardians, or both are specified in 2016-05-Supplement-04-CA-004 Health and Wellness Data Visualization Protocol.

Participants and/or parents/legal guardians are told when their physical measurements are outside values typically observed in children of similar age (Appendix U1). 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 by their health care provider, may warrant lifestyle modification).

There are potential benefits to knowing information provided by the research program. For example, information provided by the program may have personal utility to inform healthy choices to be enacted by the participant and/or their family. The family may be empowered by the knowledge provided to seek clinical care. Learning this information during childhood, when parents/legal guardians are closely involved and available to assist in understanding and contextualizing the information, may increase the potential benefit through preparation and planning.

7.3 Risk/Benefit Comparison

The foreseeable risks of this study are justified by the anticipated benefits to society through the potential for significant advancement of scientific knowledge as outlined in Section 1.5; there is also the prospect of direct benefit to pediatric participants as described in Section 7.2. The *All of Us* Research Program has potential societal benefits as a robust and diverse research resource that can facilitate the exploration of biological, clinical, social, and environmental determinants of health and disease (see Section 1.1). These benefits are anticipated to accrue exponentially over time as children are enrolled, and the dataset is used to advance future disease prevention and treatment strategies. In comparison, many of the risks are theoretical risks, and all anticipated risks and discomforts have been minimized as much as possible using risk mitigation strategies, while maintaining the potential for scientific advancement.

For pediatric populations, the benefits and risks of participating in *All of Us* are evaluated as being at least as favorable as other alternatives, which might include participation in other,

smaller registries and repositories. As a large, established program, there are more certain benefits from participating in *All of Us*, and the program has procedures developed from the enrollment of adults that help maximize the potential benefits and minimize the risks for pediatric participants (e.g., an established platform for data sharing to enable research, with robust data security to prevent misuse or loss of privacy).

Section 8: Withdrawal, Deactivation, and Permission/Assent Revocation

Pediatric participants may, at any time, stop participating in any part of the *All of Us* Research Program (or their parent(s)/legal guardian(s) may do so on their behalf) without giving a reason and without penalty. They may do this on their own by changing their participant/permission/assent status in their Participant Portal or by contacting the Support Center (Appendix W) or their HPO site, which guides them through the process. Participants and their parents/legal guardians have the option to revoke their authorization to share their EHR data. They also have the option to deactivate their account or fully withdraw from the program (see withdrawal flow in Appendix H). In addition, trained staff may deactivate (parent-/legal guardian-/participant-facing term "pause" to help indicate the individual may resume participation in the future if they meet eligibility requirements again) a pediatric participant, if necessary and for any reason, including ineligibility arising during the program (or retrospectively if overlooked at enrollment), or inappropriate actions directed toward staff. For instance, until wards of the state are eligible to participate, if we learn that a pediatric participant has become a ward of the state, we will deactivate their participation. If the program learns that another parent/legal guardian (with custodial rights) opposes the child's participation (i.e., if another parent/legal guardian notifies the program), trained staff will withdraw the child from the program (leave the program and no future use of data and biospecimens).

Consistent with the Core Protocol, pediatric participants (and/or their parents/legal guardians on their behalf) can deactivate (suspend active participation but authorize continued use of data and biospecimens) or withdraw (leave the program and no future use of data and biospecimens). Processes and protocols for deactivation and withdrawal of pediatric participants follow those specified by the current Core Protocol. Deactivation and withdrawal options can be accessed within the child's account, which is accessed via the linked parent/legal guardian's account with a workflow and communication content congruent to the adult participant experience. When pediatric participants are able to access and manage their own accounts, either the pediatric participant or a parent/legal guardian may deactivate or withdraw the participant, as both assent and permission are required for ongoing participation.

We recognize that some pediatric participants may become incarcerated, emancipated, or become wards of the state over the course of their participation in the *All of Us* Research Program. If we learn that a pediatric participant has become incarcerated or a ward of the state, we will "deactivate" (suspend active participation but authorize continued use of data and biospecimens; parent-/legal guardian-/participant-facing term "pause") their participation, until such a time as we are equipped to allow for participation by incarcerated individuals or wards of the state or until they are no longer incarcerated or a ward of the state.

We will "deactivate" (suspend active participation but authorize continued use of data and biospecimens; parent-/legal guardian-/participant-facing term "pause") the participation of both the adult and linked pediatric participant if the program learns of the following situations:

- The program learns that the linked or only parent/legal guardian for a pediatric participant becomes incarcerated.
- During Phase 1, if the linked parent/legal guardian participant becomes otherwise ineligible for adult participation according to the Core Protocol (since there is an additional pediatric eligibility criterion of having the linked parent/legal guardian be a participant in the *All of Us* Research Program).

If the pediatric participant's account becomes deactivated due to the linked parent/legal guardian leaving the program or another situation that makes the linked parent/legal guardian unable to continue in the program, then another parent/legal guardian can call the Support Center to "reactivate" the child's account. The new parent/legal guardian must have an account that can be linked to the pediatric participant's account. Parents/legal guardians who decide to deactivate a pediatric account and then reconsider that decision can likewise call the Support Center to "reactivate" the child's account, after which they may go to their account and begin the permission process.

8.1 Participant or Linked Parent's/Legal Guardian's Death

Processes for report of death and use of data and biospecimens from deceased pediatric participants will follow the current Core Protocol. The pediatric participant's account would be deactivated (suspend active participation but continue using data and biospecimens) upon the program learning of their death. If a parent/legal guardian requests no further use of the pediatric participant's data and biospecimens, the program will withdraw the pediatric participant in respect of these wishes. Individual results would no longer be available to the parents/legal guardians in the Participant Portal.

Similarly, upon the death of the parent/legal guardian who provided permission, the pediatric participant's account (and the parent's/legal guardian's account if also a participant) would be deactivated (parent-/legal guardian-/participant-facing term "paused"). Pediatric participants and/or their parent/legal guardian will be encouraged to provide a designated secondary contact who could be reached if the linked parent/legal guardian is not available. In the event that the program learns of the death of a parent/legal guardian with a linked pediatric *All of Us* account, the program would contact this secondary contact (if provided) in a respectful and sensitive manner to identify a pediatric participant's living parent(s)/legal guardian(s). The pediatric participant's living parent(s)/legal guardian(s) would have to give permission for the child's continued participation for the account to be reactivated. Alternatively, if the pediatric participant's living parent(s)/legal guardian(s) requests the child's data and biospecimen no longer be used, the program will withdraw the pediatric participant.

Processes and protocols for deactivation and withdrawal of pediatric participants follow those specified by the current Core Protocol.

8.2 Revocation of EHR Authorization

Processes for revocation of EHR authorization for pediatric participants will follow the current Core Protocol. For pediatric participants, a parent/legal guardian may revoke EHR authorization at any time. As pediatric participants reach the age of majority, at which time they can make autonomous decisions about consent and confidentiality for certain types of health care per the laws of their jurisdiction, the participant will gain sole control over sharing those records with the program as well as revoking such sharing.

8.3 Revocation of Return of DNA Results Permission/Assent (Anticipated for Future)

Processes for revocation of permission/assent for DNA results for pediatric participants will follow the current Core Protocol. Either the participant or a parent/legal guardian may revoke permission/assent to return of DNA results, which will remove access to DNA results for both parties.

Section 9: Access to Individual-Level Information for Participants

9.1 Principles of Individual-Level Information Availability

The procedures of the *All of Us* Research Program for information access adhere to principles of transparency, timeliness, and participant empowerment. Consistent with the Core Values of the program, participants have access to the individual-level data they contribute. Pediatric participants will also have readily and easily available access to the data they directly contribute. The formats and interfaces used to present these data to pediatric participants and their parents/legal guardians are described in the current Core Protocol.

9.2 Individual-Level Program Information

The types of information (data and results) gathered from and generated for pediatric participants in the *All of Us* Research Program are commensurate to those for current adult participants. Sharing of data and results with pediatric participants and/or their parents/legal guardians will follow the same principles and framework as the current Core Protocol, with additional special considerations due to the linkages between pediatric participants and their parents/legal guardians, and the special protections around pediatric privacy, particularly as children age towards and through adolescence.

For pediatric participants from birth through age 6 years, parents/legal guardians will have access to all individual-level data for the pediatric participant. The pediatric participant themselves will have access via their linked parent(s)/legal guardian(s). An amendment will be submitted to the IRB that will include delineation of which individual-level data for pediatric participants 7 years of age and older will be offered to the parent(s)/legal guardian(s) only, the pediatric participant only, or both parties. These designations may also include the opportunity for either the parent(s)/legal guardian(s) or the pediatric participant to define data sharing parameters.

9.3 Information Access Technologies

Pediatric participants and their parents/legal guardians will use the same Participant Portal platforms as adult participants. Consistent with the current Core Protocol, the Participant Portal will provide pediatric participants and their parents/legal guardians with access to their responses to PPI surveys, the values from their physical measurements, and notifications that they have provided EHR data, and potentially information about the wearables they have chosen to integrate.

9.4 Participant-Provided Information and EHRs

The program will receive various types of information about pediatric participants through surveys and other modules, including demographics, disease state, health information, lifestyle, data type, and/or location. Current program capabilities support return of individual, aggregate and comparison data for select program-approved data including self-reported survey responses. In addition, the program has deployed tools to allow for visualization and presentation of EHR data shared by participants in selected formats (i.e., Fast Healthcare Interoperability Resources format (FHIR)).

The program anticipates that our platforms will be configured so that parents/legal guardians, and the pediatric participant themself when feasible (e.g., older pediatric participants with account login credentials), will have access to information within the pediatric participant's account. The program has the capability to apply access restrictions to specific data for either adult or minor accounts and will review the need for restrictions on a case-by-case basis for protocol activities (e.g., surveys, etc.). EHR data shared by participant-mediated linkage to one or more health records providers via the Participant Portal will be integrated into the Participant Portal for participant access.

Future phases to include older children in this protocol will include delineation of which data will be offered to the parent(s)/legal guardian(s) only, the pediatric participant only, or both. These designations may also include the opportunity for either the parent(s)/legal guardian(s) or the pediatric participant to define data sharing parameters.

9.5 Access to Biospecimen-Derived Data (Non-Genetic)

As for the current Core Protocol, a wide number of assays may be performed on biospecimens. It is not possible to predict all potential types of information that may be generated, but it is anticipated to include findings within and outside of reference ranges and potentially clinically actionable information. As specific assays are planned, an information access plan with consideration for pediatric participants will be developed in tandem and submitted to the IRB for review prior to initiation of that assay.

Note that *All of Us* does not allow HIV assay or HIV testing of any type without the express consent of the participant, consistent with the law(s) of their state of residence. This approach does not prohibit the study of HIV status, as HIV status may be entered by parents/legal guardians or pediatric participants through future PPI modules or have it indicated via their EHR record or other linked data.

9.6 Access to Genomic Results

For pediatric participants who elect to contribute blood or saliva, DNA will be isolated and genomic analysis conducted for research. A separate return of genomic results permission/assent process, policies, and procedures govern the return of results from select assays (Section 4.5: Electronic Permission/Assent Documents). Additional details on the return of genomic results will be provided in a future amendment to the Appendix Q series.

Section 10: The *All of Us* Research Repository

10.1 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 is made available through the Research Hub to support scientific investigation. The DRC is responsible for aggregating, managing, and curating the data that is made accessible through the Research Hub. Data from pediatric participants will be managed per the current Core Protocol, including sections about the Raw Data Repository (RDR), Curated Data Repository (CDR), Participant Portal Data Repositories, Access to the Resource for Research, and regulations around QA/QI work and demonstration projects.

10.2 Making the Resource Accessible for Research

The *All of Us* Research Program currently provides a comprehensive resource that becomes enriched and improved over time. The program includes additional detailed longitudinal health and exposure information from pediatric participants as the protocol evolves over time and retains the flexibility to enhance its scope as funding allows.

As with the Core Protocol, data elements, including PPI, physical measurements, genomic and baseline biospecimen assays, and EHR-derived information, will be transferred through encrypted channels to the DRC for storage and for creating a dataset accessible to researchers, data security, privacy, and confidentiality will be maintained for pediatric participants, as they are for adults, and will be overseen by the Committee on Access, Privacy, and Security (CAPS), with specific consideration of adult-child linkages.

The pediatric data will be included in the researcher-accessible dataset, which is queried through a dedicated analysis platform, the *All of Us* Research Hub, for research purposes. The DRC will develop tools to enable analysis of the pediatric and family data within this secure cloud-computing environment. Qualified researchers who wish to access the data agree to not remove data. The *All of Us* Research Program brings researchers to the data rather than asking researchers to download data to their own machines. The CAPS serves as the stewards of the data and will similarly serve as stewards of the pediatric and family data.

10.3 *All of Us* Data Access Governance

All of Us data access governance, as specified by the current Core Protocol, will apply to all data obtained for pediatric participants. Regulation and protocols for data access and use, including data tiers, are specified in the Core Protocol, including the requirement for additional approvals for studies that require information such as exact birth dates, which may be relevant for some

pediatric research studies. Genomic data sharing, import of external data, access and use of biospecimens, and contact of participants for pediatric participants is commensurate with the Core Protocol.

10.4 Confidentiality, Privacy, and Security

As with adults, maintaining data security and privacy within the *All of Us* Research Program is paramount to maintaining the trust and engagement of pediatric participants and their parents/legal guardians. All of the extensive regulations, policies, governance, compliance, and technical safeguards outlined in the Core Protocol and implemented by the current program to ensure data security and privacy also apply to data from pediatric participants.

Section 11: Post-Enrollment Engagement Strategy

The post-enrollment engagement strategy for pediatric participants, consistent with the current Core Protocol, is focused on empowering pediatric participants, families, and communities through greater access to information and data. These efforts increase the value of the program for pediatric participants, the quality of the data for research, and the positive impact of the program on society.

11.1 Approach to Engagement

Engagement in the *All of Us* Research Program is defined as a broad range of relationship-building bidirectional interactions, including information sharing, consultation, collaboration in decision making, and empowered action between the program, people, awardees, and other partners. It is a systematic, considered process, with the express purpose of working with groups of people 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.

The engagement strategy is designed to encourage multidirectional communication and participation in the program by individuals—those participating, their advocates, and interested community members—and organizations. Engagement strategies are threaded through awareness, enrollment, and retention activities. To facilitate pediatric participation and family-based enrollment, the entire current engagement pipeline will be leveraged.

The program's National Community Engagement Partners, including the National Alliance for Hispanic Health, Asian Health Coalition, Stanford University School of Medicine/PRIDEnet, Network of the National Library of Medicine (NNLM), Delta Research Educational Foundation, and American Association on Health and Disability, are well equipped to engage pediatric participants and community stakeholders to facilitate engagement across the lifespan, including infancy, childhood, and adolescence. In addition, in partnership with the *All of Us* Engagement Core at Vanderbilt University Medical Center, the program will continue to elevate participant voices from diverse communities throughout the program by 1) identifying Pediatric Champions to join the Steering Committee and Executive Committee and 2) establishing the *All of Us* Youth and Family Committee, a pediatrics-focused group primarily composed of parents/legal guardians or those who have expertise in pediatrics or pediatric research as well as teens and

young adults. Additional community engagement partners could be funded to conduct similar activities to further support additional pediatric engagement and enrollment.

An engagement partner, University of Utah, has created and will continue to create hands-on activities, including educational materials for families (Appendices R1–R4). These can be used with individuals, in small groups, or at large events. These engagements were developed by the Genetic Science Learning Center (GSLC) at the University of Utah with multiple rounds of feedback from a community Validator's Group, the *All of Us* Engagement Incubator, and Subject Matter Experts. The GSLC has almost 30 years of experience developing educational materials for K-12 students and teachers, families, patients, and the public. To further support pediatric engagement, the University of Utah team will develop a pilot for museum based *All of Us* outreach powered by Utah engagements, programming, and museum staff training. This will help raise awareness around the program with future pediatric participant families who will learn about the program through fun activities and will be interested to enroll with their children. The University of Utah team will also hold listening sessions with museums to determine their interest in displaying *All of Us* materials as engagement materials for the general public in learning about precision health and engagements for families and children to do together.

11.2 Retention

Long term retention of pediatric participants in the *All of U*s Research Program is an important and significant challenge. Given the dynamic periods of growth and development during infancy, childhood, and adolescence, the longitudinal data generated by a large, diverse cohort of pediatric participants has the potential to support tremendous scientific breakthroughs to inform health during childhood and beyond. The growth and development of pediatric participants also provides opportunities for dynamic and age-specific interactions of pediatric participants and their families with the program, fostering successful relationship building and retention.

Strategies for pediatric retention include the digital and non-digital approaches described in the current Core Protocol. Any awardee institution wishing to use approaches to retention (i.e., methods specifically designed for pediatric participants) other than those described here will submit their site-specific plans to the IRB as part of the ISIA.

Section 12: Site Monitoring, Reporting, and Training

Pediatric participation in the *All of Us* Research Program will be overseen by entities and processes chartered by the Core Protocol, including:

- A central IRB specific to the *All of Us* Research Program
- The *All of Us* Research Program Research Compliance Branch and other contract organizations that support regulatory compliance
- The *All of Us* Research Program Advisory Panel (which includes members with pediatric and family expertise)
- Robust quality assurance procedures
- A governance structure that includes working groups and incorporates participants in all aspects

- Partner-specific participant boards

12.1 Handling On-Site Reportable Events

Unexpected adverse events and unanticipated problems (reportable events) are reported to *All of Us* and the IRB in accordance with HHS requirements for disclosing reportable events and unanticipated problems. As with the Core Protocol, *All of Us* Research Program clinical partners provide applicable accreditations, policies, and procedures—and ensure relevant training of program staff—to ensure appropriate processes are in place for responding to situations when physically working with the *All of Us* Research Program pediatric participants. These policies and procedures are collected by the *All of Us* Program Officers and filed as part of a site's ISIA.

12.2 Monitoring Enrollment

Consistent with the current Core Protocol, pediatric enrollment will be monitored with respect to total number enrolled, and across demographics such as age, race/ethnicity, and other UBR status metrics. Initial enrollment goals for race/ethnicity distribution of pediatric participants in the *All of Us* Research Program are consistent with current enrollment goals for the program as a whole.

Measures described in the Core Protocol, including the enrollment-monitoring plan, mitigating actions for under-enrollment, and site-based adjustment of recruitment efforts, will apply to pediatric enrollment.

12.3 Training Expectations

For pediatric enrollment, all training mandates, methods, documentation described in the Core Protocol apply. For pediatric enrollment, all training mandates, methods, documentation described in the Core Protocol apply. Staff involved with pediatric enrollment will be required to be up to date on the annual *All of Us* Consortium Training course or refresher (note, training is not pediatric-specific).

In addition, pediatric-specific training will include:

- Read the Pediatric Supplemental Protocol
- Read all relevant pediatric Standard Operating Procedures (SOPs)
- Complete a Pediatric Supplemental Protocol Training Module
    - This training will educate staff on the overall pediatric protocol including how to describe differences between adult and pediatric participation. Topics will cover pediatric eligibility and provide an overview of the enrollment process including biospecimen collection and physical measures, as well as train staff on how to respond to out-of-range results. Links will be included to guide staff to relevant SOPs and job aids.
    - This training will include specific training in obtaining Parental Permission and Recognizing Dissenting Behavior, providing staff with skills for recognizing the difference between dissenting behavior and typical age-related responses and strategies to prevent and respond to dissenting behaviors.

Section 13: References

1. The Child Enrollment Scientific Vision Working Group Report to the *All of Us* Research Program Advisory Panel; 2017. https://allofus.nih.gov/sites/default/files/cesvwg_1-18-18.pdf. Accessed January 31, 2023.
2. Galbraith S, Bowden J, Mander A. Accelerated Longitudinal Designs: An overview of modelling, power, costs and handling missing data. *Statistical Methods in Medical Research*. 2016;26(1):374-398. https://doi.org/10.1177/0962280214547150
3. Shonkoff JP. Leveraging the biology of adversity to address the roots of disparities in health and development. *Proc Natl Acad Sci USA*. 2012;109 Suppl 2(Suppl 2):17302-17307. https://doi.org/10.1073/pnas.1121259109
4. Braveman P, Barclay C. Health disparities beginning in childhood: A life-course perspective. *Pediatrics*. 2009;124(Supplement_3):S163-S175. https://doi.org/10.1542/peds.2009-1100d
5. Romano ME, Buckley JP, Elliott AJ, Johnson CC, Paneth N. SPR Perspectives: Scientific Opportunities in the environmental influences on Child Health Outcomes Program. *Pediatric Research*. 2021;92(5):1255-1261. https://doi.org/10.1038/s41390-021-01577-5
6. Mapes BM, Foster CS, Kusnoor SV, et al. Diversity and inclusion for the *All of Us* research program: A scoping review. *PLoS One*. 2020;15(7):e0234962. Published 2020 Jul 1. https://doi.org/10.1371/journal.pone.0234962
7. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA*. 2009;301(21):2252-2259. https://doi.org/10.1001/jama.2009.754
8. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*. 2007;447(7145):661-678. https://doi.org/10.1038/nature05911
9. Visscher PM, Wray NR, Zhang Q, et al. 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet*. 2017;101(1):5-22. https://doi.org/10.1016/j.ajhg.2017.06.005
10. The Child Enrollment Scientific Vision Working Group Report to the *All of Us* Research Program Advisory Panel. Ibid.
11. Hofferth SL, Stafford FP, Yeung W-JJ, et al. Panel Study of Income Dynamics, 1968-1999: Supplemental files (ICPSR 3202). openICPSR. https://www.openicpsr.org/openicpsr/project/127981/version/V1/view Published December 4, 2020. Accessed January 31, 2023.
12. Mills MC, Rahal C. The GWAS Diversity Monitor tracks diversity by disease in real time. *Nat Genet*. 2020;52(3):242-243. https://doi.org/10.1038/s41588-020-0580-y

13. Office for Human Research Protections, HHS.gov. “How do the regulations define “prisoner”? Prisoner Research FAQs. https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/prisoner-research/index.html Accessed February 10, 2023.
14. Brown HR, Harvey EA, Griffith SF, Arnold DH, Halgin RP. Assent and dissent: Ethical considerations in research with Toddlers. Ethics & Behavior. 2017;27(8):651-664. https://doi.org/10.1080/10508422.2016.1277356
15. Varma S, Wendler D. Research involving wards of the state: protecting particularly vulnerable children. *J Pediatr*. 2008;152(1):9-14. https://doi.org/10.1016/j.jpeds.2007.07.039
16. Feinberg J. The child’s right to an open future. In: Aiken W, LaFollette H, eds. *Whose Child? Children’s Rights, Parental Authority, and State Power*. Rowman and Littlefield; 1980:124-153.

Section 14: List of Terms and Acronyms

ACEs	Adverse Childhood Experiences
ADHD	Attention-Deficit/Hyperactivity Disorder
AHRQ	Agency for Healthcare Research and Quality
AI/AN	American Indian and Alaska Native
CAPS	Committee on Access, Privacy, and Security
CATI	Computer Assisted Telephone Interviewing
CDR	Curated Data Repository
CESVWG	Child Enrollment Scientific Vision Working Group
COPPA	Children's Online Privacy Protection Act
DNA	Deoxyribonucleic Acid
DRC	Data and Research Center
EHR	Electronic Health Record
ELSI	Ethical, Legal and Social Implications
FQHC	Federally Qualified Health Centers
GCR	Genetic Counseling Resource
GSLC	Genetic Science Learning Center
GWAS	Genome-Wide Association Studies
GxE	Gene-Environment interactions
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HPOs	Health care Provider Organizations
IRB	Institutional Review Board
ISIA	Institution-Specific IRB Application
LGBTQ+	Lesbian, Gay, Bisexual, Transgender, Queer, and/or Questioning
NIH	National Institutes of Health
NQF	National Quality Forum
PID	Participant Identifier
PM	Physical Measurement

PM&B	Physical Measurement and Biospecimen
POTF	Pediatric Operations Task Force
PPI	Participant-Provided Information
PSVTF	Pediatric Scientific Vision Task Force
PTSC	Participant Technology Systems Center
RDR	Raw Data Repository
SGM	Sexual Gender Minority
SMS	Short Message/Messaging Service
TPC	The Participant Center
UBR	Underrepresented in Biomedical Research
VA	Veterans Affairs

Section 15: Applicability of Core Protocol Appendices to Pediatric Supplement

Note: The appendices referenced throughout the protocol and listed in Sections 15 and 16 are subject to change as we align the Pediatric Protocol with the Core Protocol version 2.0 amendment.

Core Protocol Appendix	Content	Applicable to Pediatrics?
B	Enrollment numbers [will be retired]	No
C1	Outreach strategy and Engagement Framework	No
C_P1	Pediatric Asset Development Strategy	Yes
C2	Ad Campaign	No
C3	Website Copy	Yes
C4	App Copy	No
C_P4	Pediatric Portal User Experience	Yes
C5	Video Materials	No
C6	Partner Toolkit	Yes
C7	Testimonials	Yes
C10	Genomics Communication	No
C11	eConsent speed warning screens	Yes
C12	AI/AN Communications	Yes
C13	COVID-related Messaging	No
C14	CATI	Yes
C15	Mental Health & Wellbeing Campaign	No
C16	*All of Us* Data, Thanks to You	Yes
C17	Social Determinants of Health	No
C18	Refer a Friend	Yes
D	General FAQs	Yes
D_P1	Pediatrics FAQs	Yes
E1	Primary Consent	No
E_P1	ePermission to Participate birth to 6	Yes
E_P2	EHR/Part 2 eConsent and HIPAA authorization	Yes
E_P3	ePermission for Return of DNA Results birth to 6	Yes
E4	Physical Measurements-Biosample eConsent Refresher Loop	No
E8	Return of DNA Research Results eConsent	No
E10	Reconsent [will be renumbered to E6]	Yes

Core Protocol Appendix	Content	Applicable to Pediatrics?
TBD	Assent to Participate (will be created in future)	Yes
TBD	Assent for Return of DNA Results (will be created in future)	Yes
F1	Primary Consent Form	No
F_P1	Permission to Participate longform birth to 6	Yes
F_P2	Permission for DNA Results longform birth to 6 (will be created in future)	Yes
F2 (except for F2-VA)	EHR/Part 2 eConsent and HIPAA authorization	Yes
F3	California Bill of Rights	Yes
F4	gRoR Consent Form	No
G1	Overall Health module	No
G2	Lifestyle module	No
G3	Basics module	No
G4	Health Access module	No
G6	Personal and Family Health History module	No
G7	Mental Health module	No
G8	COVID module	No
G9	Social Determinants of Health module	No
G10	Remote PM module	No
G11	PPI-Life Functioning Module	No
G13	Biospecimen Screens and Survey	Yes
G14	ID Verification	No
G_P1	Basics Birth to 6 module	Yes
G_P2	Overall Health Birth to 6 module	Yes
G_P3	Environmental Exposures Birth to 6 module	Yes
H	Withdrawal screens	Yes
J1	Framework for Engagement & Retention Tools	Yes
J2	Snap questions	No
J3	General email/SMS/letter Messages	No
J_P3	Pediatric Emails, SMS, Letters, and Messages	Yes
J4	HPO Scripts	No
J5	Customizable Messaging	Yes
O1 & O2	DHT Umbrella Protocol	No
P	Translation Process	Yes
Q1	Genomics Communications	No

Core Protocol Appendix	Content	Applicable to Pediatrics?
Q_E	Genetic Ancestry and Traits	No
Q_H	Health-related Genomics	No
R1	General and biobank-related engagements	No
R2	Viruses/vaccine engagements	No
R3	Genomics engagements - Multimedia Scripts	No
R4	Genomics engagements - Hands-on Activities	Yes
R5	Engagement Innovators: PRIDEnet	No
S	Learning Center - Genomics	No
T1	Biospecimen Collections, Shipment, and Storage.	Yes
T2	Biospecimen Communications	Yes
U1	Physical Measurement Collections	Yes
U2	Physical Measurement Communications	Yes
V1	Ancillary Studies	Yes
V2	Nutrition for Precision Health	No
W	Support Center	Yes
W2	Support Center Communications (in development)	Yes

Section 16: Tables of Future Pediatric Protocol and Core Protocol Appendix Amendments

Note: Appendices in Section 15 that are not anticipated to need revisions for pediatric enrollment are not listed in this section. The current content of the Core Protocol appendix is applicable to pediatric as well as adults.

Note: The appendices referenced throughout the protocol and listed in Sections 15 and 16 are subject to change as we align the Pediatric Protocol with the Core Protocol version 2.0 amendment.

Core Protocol Appendices

Core Protocol Appendix	Content	Anticipated Submission
C_P1	Pediatric Asset Development Strategy	Submitted to IRB 8/31/2023
C_P4	Pediatric Portal User Experience	Submitted to IRB 9/12/2023
C6	Partner Toolkit	Future
C10	Genomics Communication	Future
C14	CATI	Submitted to IRB 8/31/2023
D	General FAQs	Submitted to IRB 9/12/2023
D_P1	Pediatrics FAQs	Submitted to IRB 10/2/2023
E_P1	ePermission to Participate	Submitted to IRB 7/31/2023
E_P2	EHR/Part 2 eConsent and HIPAA authorization	Submitted to IRB 8/4/2023
E_P3	ePermission for Return of DNA Results	Future; Video scripts/storyboards submitted to IRB 7/31/2023
TBD	Assent to Participate	Prior to Phase 2
TBD	Assent for Return of DNA Results	Future
E10	Reconsent	Future if necessary
F2 series (except for F2-VA)	EHR/Part 2 eConsent and HIPAA authorization	Submitted to IRB 8/4/2023
F_P1	Permission to Participate	Submitted to IRB 7/31/2023
F_P2	Permission for Return of DNA Results	Future
TBD	Assent to Participate	Prior to Phase 2

Core Protocol Appendix	Content	Anticipated Submission
TBD	Assent for Return of DNA Results	Prior to Phase 2
G_P1	Basics Birth to 6 module	Submitted to IRB 9/11/2023
G_P2	Overall Health Birth to 6 module	Submitted to IRB 9/11/2023
G_P3	Environmental Exposures Birth to 6 module	Submitted to IRB 9/11/2023
H	Withdrawal screens	Submitted to IRB 8/4/2023
J_P3	Pediatric Emails, SMS, Letters, and Messages	Submitted to IRB 9/12/2023
J5	HPO Scripts	Future
Q1	DNA Results Protocol	Submitted to IRB 6/22/2023 but withdrawn 9/7/2023. Resubmission planned after micro-launch
Q_H series	Health-related Genomics	Future
T1	Biospecimen Collections, Shipment, and Storage	Submitted to IRB 5/29/2023
T2	Biospecimen Communications	Submitted to IRB 9/12/2023
U1	Physical Measurement Collections	Submitted to IRB 5/29/2023
U2	Physical Measurement Communications	Submitted to IRB 9/11/2023
V1	Ancillary Studies	Future

Protocol Sections

Protocol Section	Content	Anticipated Submission
Synopsis	Future phases (Phases 2 and 3) extending enrollment to enable participation of additional age groups and/or participation of individuals under the age of majority without an associated adult participant.	Prior to Phases 2 and 3
1.5.4, 4.5, and 9.6	The plan for genetic return of results for pediatric participants and their families. Edits throughout the protocol to remove references to the return of DNA results in the future.	Future
3.1 and 3.3	Outreach materials will be developed specifically to reach older children in later phases.	Prior to Phases 2 and 3
3.5	Any MEA materials describing pediatric participation in *All of Us*	Future

Protocol Section	Content	Anticipated Submission
4.4.2	A description of the assent process and site staff training around assent	Prior to Phases 2 and 3
4.4.6	A description of the timing and process for requesting permission and assent at ages 7 and 13 years. A description of the process for requesting consent and requests for any necessary waivers of consent/at age of majority	Prior to Phase 2 and 3
4.5	Approach(es) to obtaining assent and a description of the methods used for indicating assent. The age at which the program will require assent for return of DNA results.	Prior to Phases 2 and 3
4.7	Plans to enroll vulnerable participants, such as wards of the state, prisoners, and cognitively impaired minors	Future
4.7.1	A monetary compensation strategy for pediatric participants ages 13 years to age of majority	Prior to Phase 3
4.7.8	Provisions for continued participation and enrollment of children with cognitive disabilities who are age 7 years and older (who may be unable to participate in assent activities designed for typically developing children and adolescents)	Prior to Phase 2
5.1	New surveys will be submitted to the IRB for review and approval prior to implementation.	Future
5.5	Addition of any new data sources linked to the program's dataset	Future
5.5	Any linkages that require the DRC to share participant-identifying information to an outside entity	Future
9.2	Delineation of which individual-level data will be offered to the parent(s)/legal guardian(s) only, the pediatric participant only, or both for participants 7 years of age and older.	Prior to Phases 2 and 3
9.4	Future phases to include older children in this protocol will include delineation of which data will be offered to the parent(s)/legal guardian(s) only, the pediatric participant only, or both.	Prior to Phases 2 and 3
9.5	As specific assays are planned, an information access plan with consideration for pediatric participants will be developed in tandem	Future

Section 17: Protocol Versions

Version	Date	Significant revisions
v1.0	20Apr2023	Initial IRB Submission