# HEALthy Brain and Child Development Study

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CRAN Council
May 8, 2024

HEALthy Brain and Child Development
Babies · Brains · Bright Futures

# What is HBCD?

HEALthy Brain and Child Development
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- Ten year longitudinal study
- Enrollment starting in 2nd trimester of pregnancy
- Multi-modal assessments of brain, cognitive and emotional development from birth through childhood
- Characterize neurodevelopmental trajectories from large sample (~7,000)
- Determine how substance exposure and other environmental factors affect developmental trajectories
- Yearly data release beginning in late 2024/early 2025

# HBCD Support

National Institute on Drug Abuse (NIDA)

National Institute of Mental Health (NIMH)

National Cancer Institute (NCI)

National Institute of Neurological Disorders and Stroke (NINDS)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

National Institute of Environmental Health Sciences (NIEHS)

National Institute on Minority Health and Health Disparities (NIMHD)

Office of Behavioral and Social Sciences Research (OBSSR)

Office of Research on Women's Health (ORWH)

National Eye Institute (NEI)

NIH HEAL INITIATIVE

# HBCD Consortium

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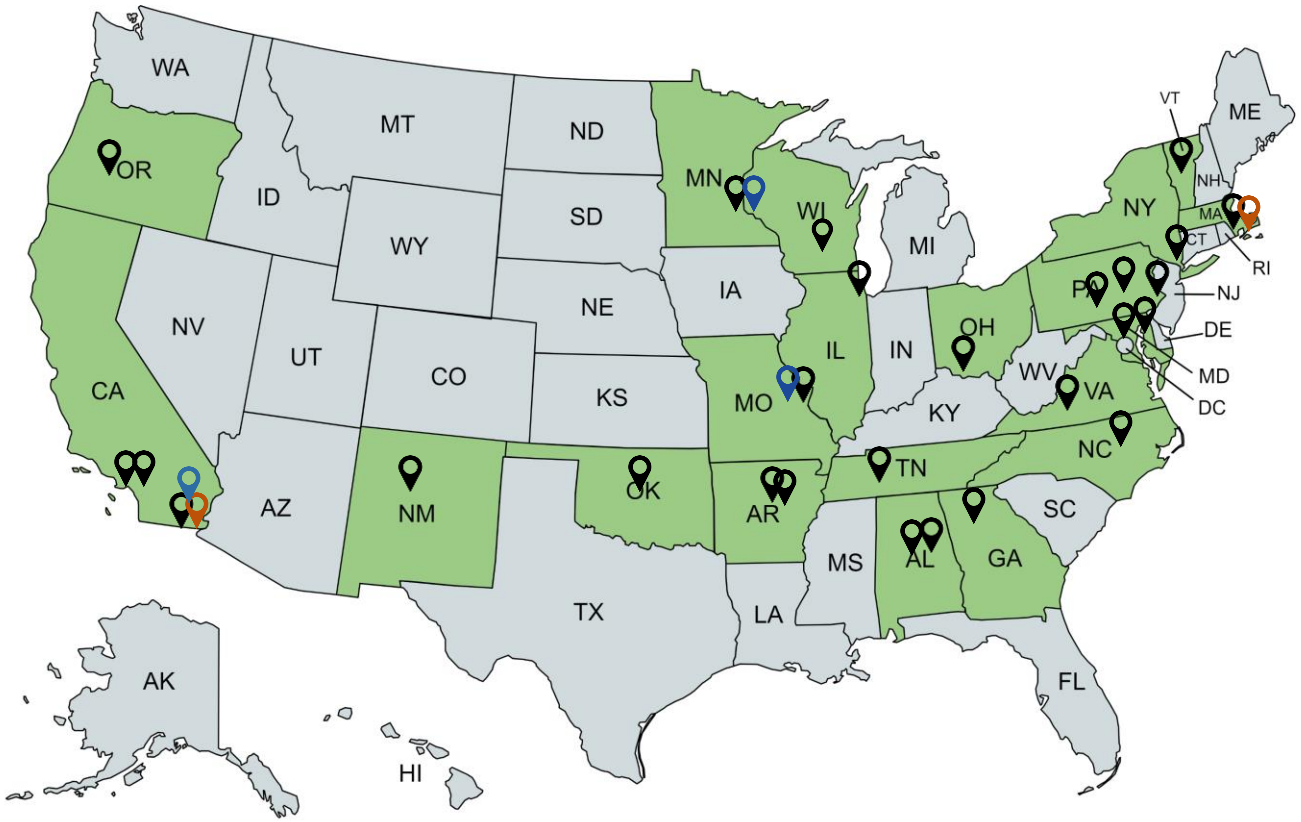


HBCD Recruitment Site
HBCD Consortium Administrative Core (HCAC)
HBCD Data Coordinating Center (HDCC)

Arkansas Children's Hospital
***Boston Children's Hospital
Cincinnati Children's Hospital
Children's Hospital Los Angeles/University of Southern California
Cedars Sinai Medical Center
Children's Hospital of Philadelphia
Emory University
Johns Hopkins University
New York University
Northwestern University
Oregon Health Sciences University
Oklahoma State University
Pennsylvania State University State College
Pennsylvania State Hershey Medical Center
University of Alabama Birmingham
University of Alabama Tuscaloosa
University of Arkansas Medical School
University of Maryland
***University of Minnesota
University of New Mexico
University of North Carolina
*** ***University of California San Diego
University of Vermont
University of Wisconsin Madison
Vanderbilt University
Virginia Tech University
*** Washington University St Louis

# HBCD Study Objectives

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- What are **typical neurodevelopmental trajectories** and what is the normal range of variability in brain development from birth through childhood? How do biological and other environmental exposures affect these developmental trajectories
- How do **genetic influences** interact with **environmental factors** to influence neurodevelopment and cognitive, emotional, and social behavior?
- How does early life exposure to **opioids, other substances**, and/or **other adverse environmental circumstances** affect developmental trajectories?
- Are there **key developmental windows** during which the impact of **adverse exposures** (e.g., stress, COVID 19) influence later neurodevelopmental outcomes?
- Are there **key developmental windows** during which **ameliorating influences** (e.g., substance use disorder treatment; social/economic support) are protective against the potential neurodevelopmental insults of early adverse exposures?
- What is the impact of early **parent/caretaker interactions** with their children on later health and other outcomes?

Prenatal Health
Substance-use
Trauma
Perceived Stress
Protective Factors

Pre-pregnancy Factors

Social and Environmental Determinants

Early Life Stress
Environmental Exposures
Poverty
Discrimination
Access to Resources

Physical Health
Genetics
Nutrition
Epigenetics
Microbiome

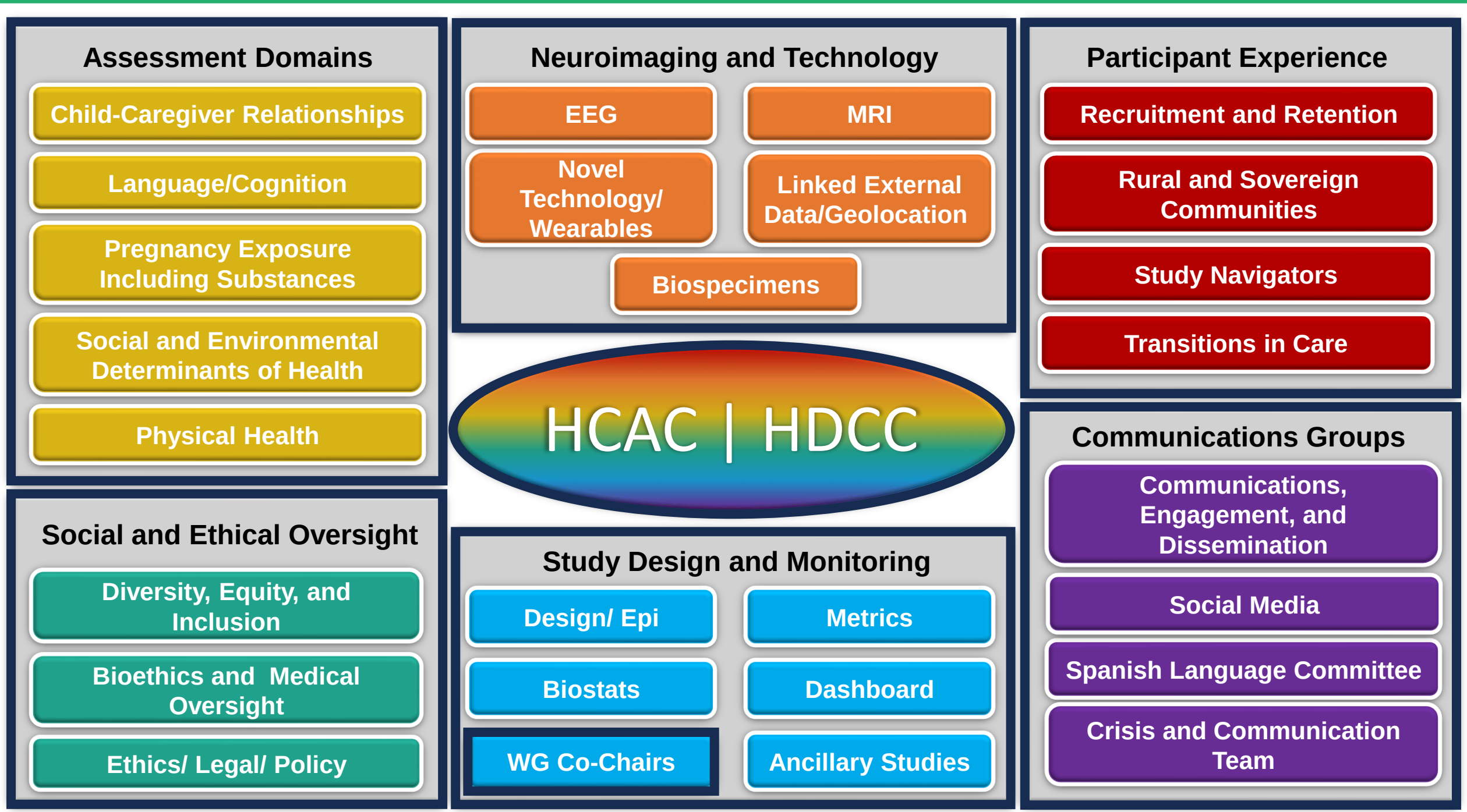
Biological Factors

Parent/Child Factors

Child-Caregiver Relationship
Behavioral Regulation
Mental Health
Home Environment

Child Cognition and Neurodevelopment

DEVELOPMENT


Assessment Domains
Child-Caregiver Relationships
Language/Cognition
Pregnancy Exposure Including Substances
Social and Environmental Determinants of Health
Physical Health
Social and Ethical Oversight
Diversity, Equity, and Inclusion
Bioethics and Medical Oversight
Ethics/ Legal/ Policy
Neuroimaging and Technology
EEG
MRI
Novel Technology/ Wearables
Linked External Data/Geolocation
Biospecimens
HCAC | HDCC
Study Design and Monitoring
Design/ Epi
Metrics
Biostats
Dashboard
WG Co-Chairs
Ancillary Studies
Participant Experience
Recruitment and Retention
Rural and Sovereign Communities
Study Navigators
Transitions in Care
Communications Groups
Communications, Engagement, and Dissemination
Social Media
Spanish Language Committee
Crisis and Communication Team

# HEALthy Brain and Child Development Study

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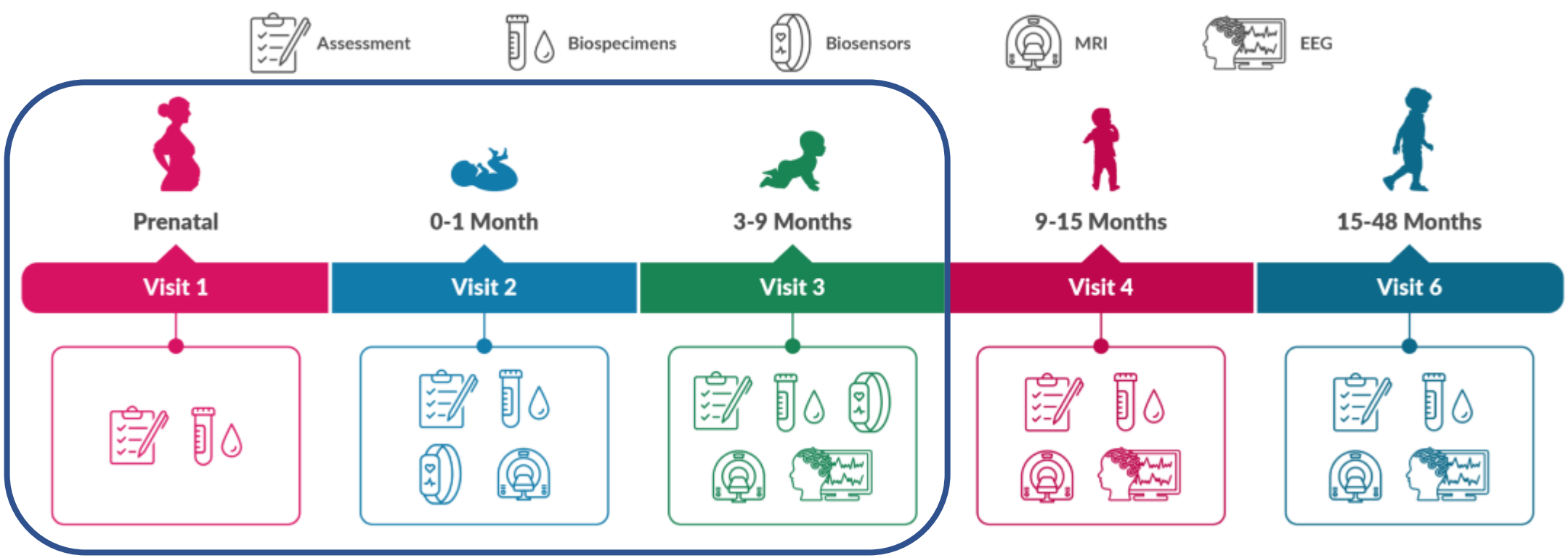
## Timeline of Events




Remote assessments will take place at visits **5** (10-17 months), **7** (16-50 months), and **8** (36-60 months).

# Protocols: Visit 1-2

## Visit 1: Prenatal

### Maternal Health
- APA DSM-5 Level 1
- APA PROMIS Level 2
- DSM-5 Severity Acute Stress
- DSM-5 Severity PTSD
- Edinburgh Postnatal Depression Scale (EPDS)
- Family History Assessment Module (FHAM)
- Health History

### Biospecimens
- Maternal Blood
- Maternal Nails
- Maternal Saliva
- Maternal Urine

### Substance Use
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
- Timeline Followback (TLFB)

### Culture & Environment
- BFY Services/Support
- BFY Economic Stress
- Demographics
- Intimate Partner Violence (E-HITS)
- PROMIS Social Support
- PROMIS Perceived Stress
- Protective and Compensatory Experiences (PACES)
- PhenX Discrimination
- PhenX Neighborhood Safety
- Work-related Environmental Exposures

## Visit 2: 0-1 Month

### Adult Health
- APA DSM-5 Level 1
- APA PROMIS Level 2
- DSM-5 Severity Acute Stress
- DSM-5 Severity PTSD
- Edinburgh Postnatal Depression Scale (EPDS)
- Health History

### Biospecimens
- Child Saliva
- Child Stool
- Child Urine
- Maternal Nails
- Maternal Saliva

### Substance Use
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)
- Timeline Followback (TLFB)

### Culture & Environment
- PROMIS Social Support
- PROMIS Perceived Stress

### Child Health
- Head Circumference
- Health History
- Height
- Weight

### Nutrition
- 2-Item Food Insecurity Screen
- PhenX Breastfeeding Questionnaire

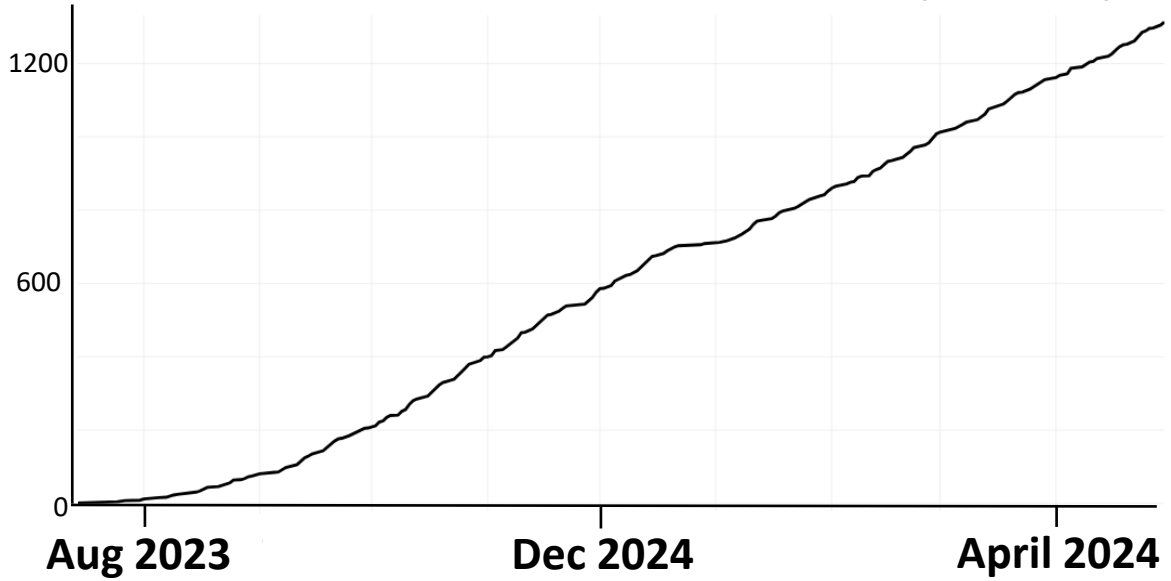
### Mobile Technology
- Activity Surveys
- Heart Rate Sensors
- Movement Sensors

### Brain Imaging
- Diffusion MRI
- Functional MRI
- MR Spectroscopy
- Quantitative MRI
- Structural MRI (T1/T2)

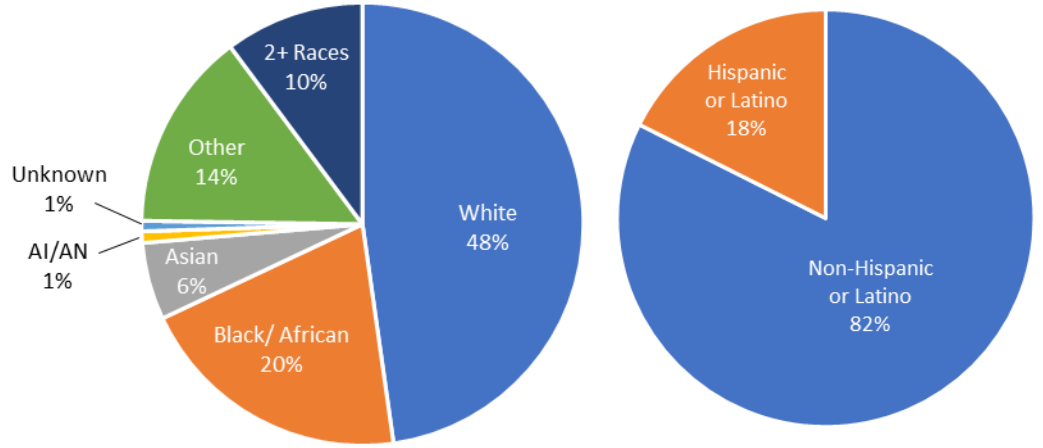
# Protocols: Visit 3

# HBCD Enrollment and Timelines

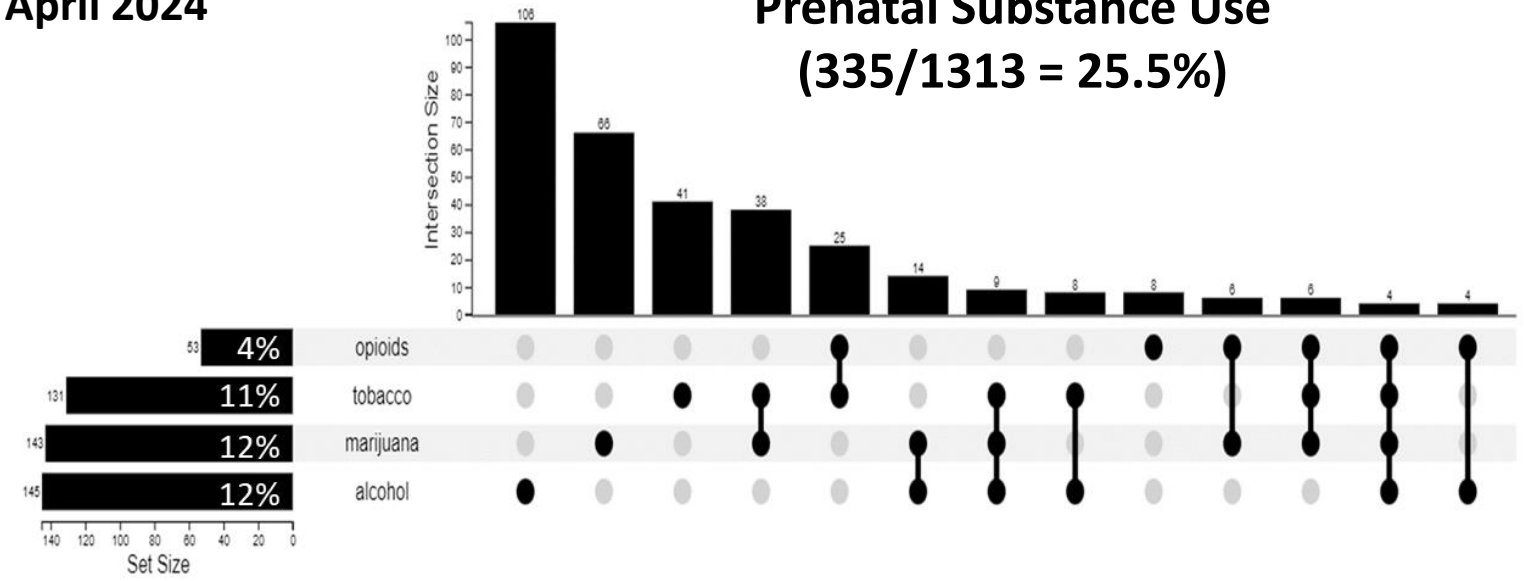
## Prenatal Enrollment Across 27 Sites (N=1313)




## Race and Ethnicity




## Prenatal Substance Use (335/1313 = 25.5%)




### Prenatal Substance Use Criteria

**Opioids:** ≥Weekly for ≥2 weeks
**Tobacco/Nicotine:** ≥Weekly for ≥4 weeks
**Marijuana/Cannabis:** ≥Weekly for ≥4 weeks
**Alcohol:** ≥7 standard drinks/week for ≥2 weeks; or ≥3 standard drinks/occasion on ≥2 occasions

# Neuroimaging Modalities – MRI & EEG

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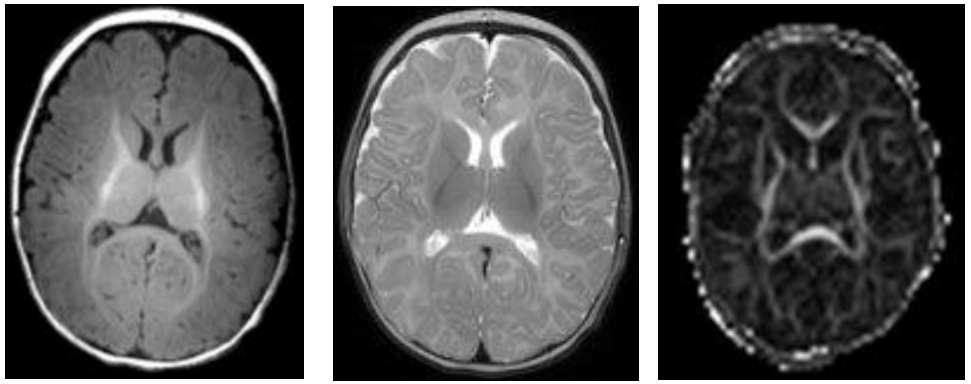
MRI Scans:

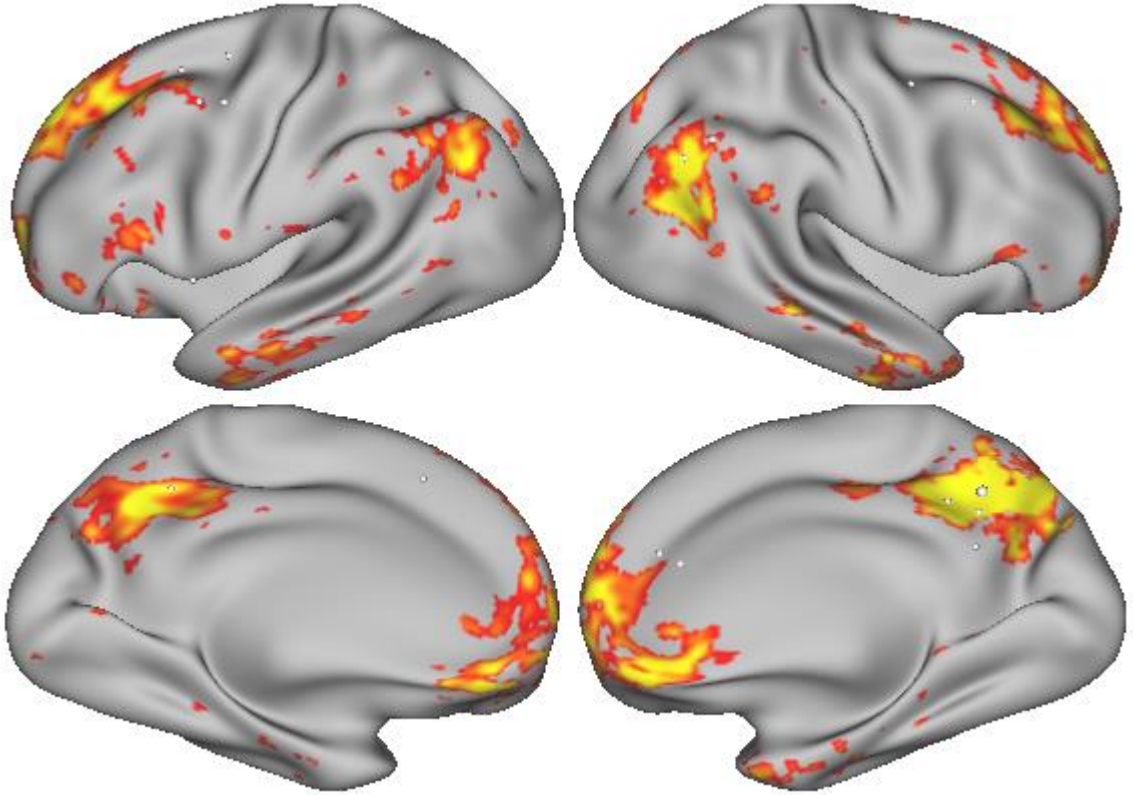
- Structural Scans (T1 and T2)
- Diffusion MRI
- Quantitative MRI
- Functional MRI
- Spectroscopy



T1 T2 dMRI

**Default System at Birth**

First HBCD Infant (Visit 2)



# Neuroimaging Modalities – MRI & EEG

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MRI Scans:

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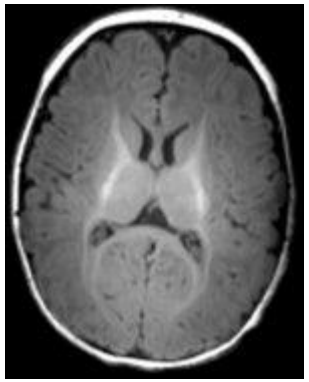
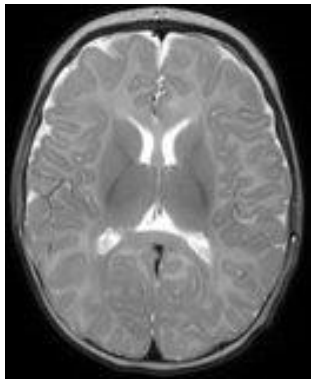
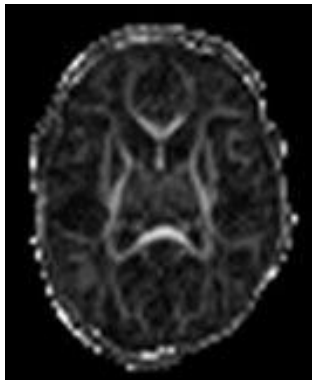


T1



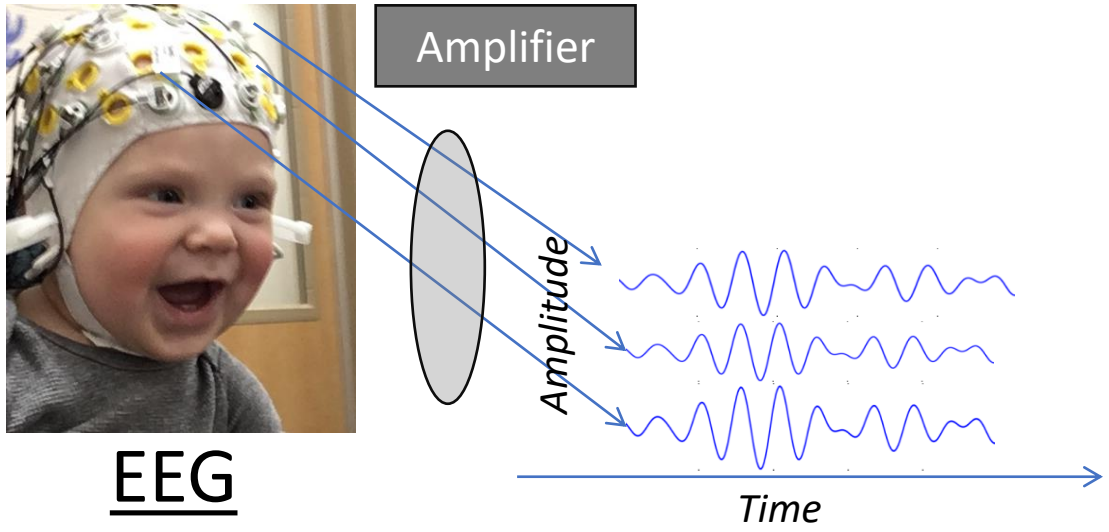
T2



dMRI

EEG Domains:

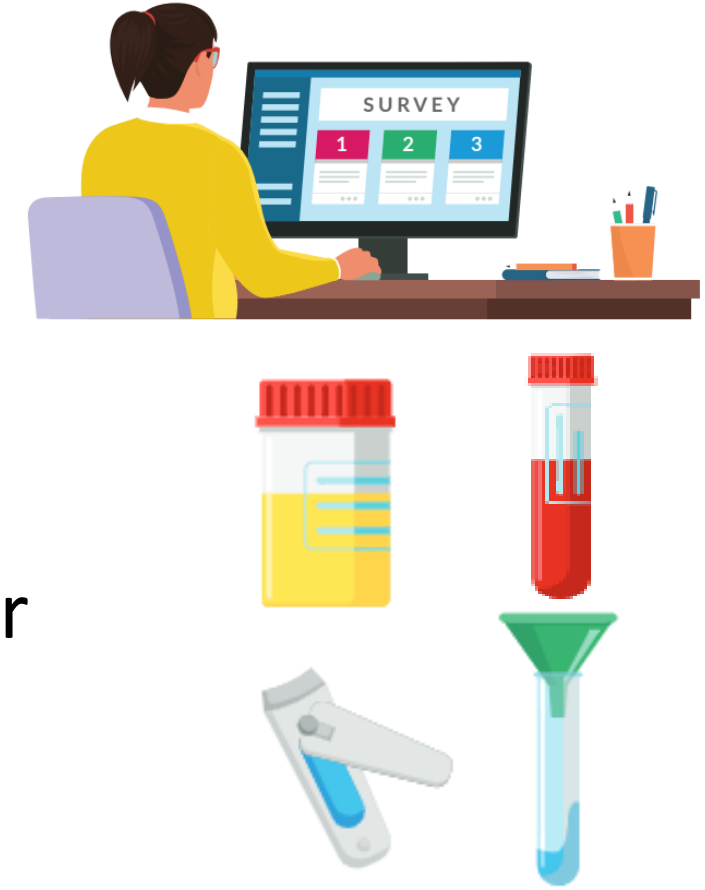
- Resting State/ Baseline
- Response to Faces
- Visual Evoked Potentials
- Auditory Oddball/ MMN




EEG

# Substance Use Measures

- Substance use is assessed before, during and after pregnancy
- Captured through self-report (Assist and Timeline Follow Back) and analysis of biospecimens
- Thresholds are used for enrollment targets for opioids, alcohol, nicotine and cannabis

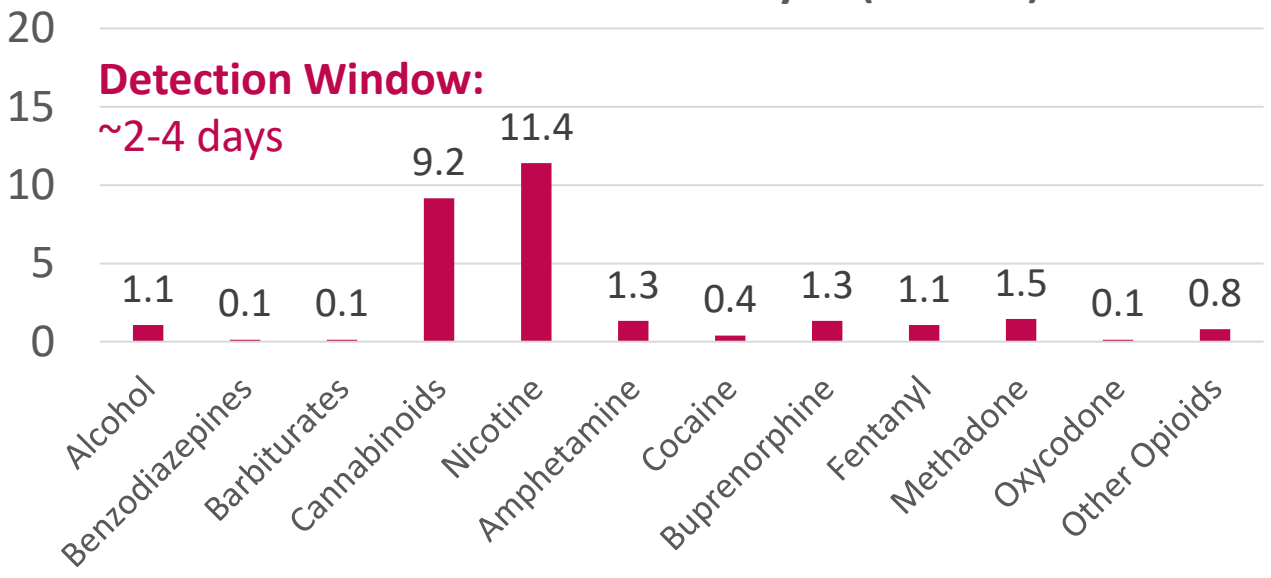


# HBCD Biosampling by Visit

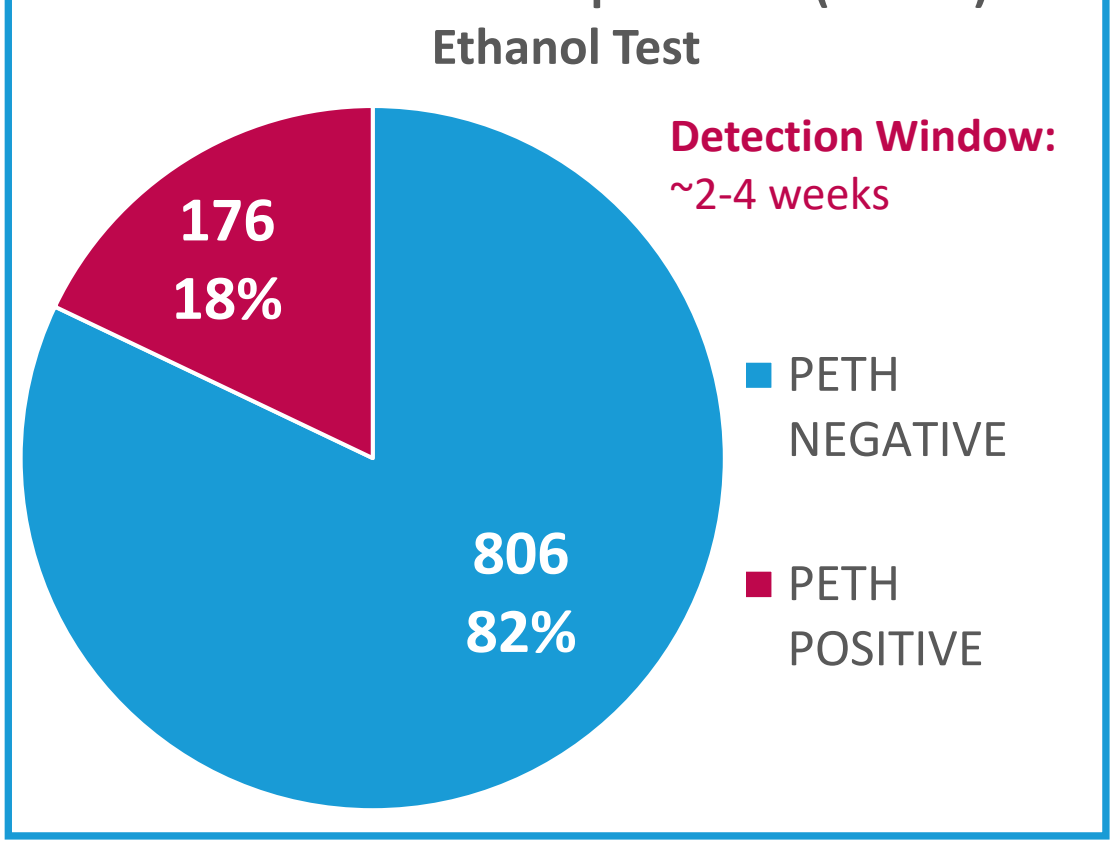
| Sample | Visit | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1<br>Prenatal | 2<br>0-1 Month | 3<br>3-9 Months | 4<br>9-15 Months | 5<br>10-17 Months | 6<br>15-48 Months | 7<br>16-50 Months | 8<br>36-60 Months |
| **Maternal Samples** | | | | | | | | |
| Nails (Toenails ~120 mg) | ✓ | ✓ | | | | | | |
| Blood (Serum, Plasma, Whole Blood) | ✓ | | | | | | | |
| Urine (~50 ml) | ✓ | | | | | | | |
| Saliva (1 collection) | ✓ | | | | | ✓ | | |
| **Child Samples** | | | | | | | | |
| Urine (~5 ml) | | ✓ | ✓ | ✓ | | ✓ | | |
| Stool (2 devices) | | ✓ | ✓ | ✓ | | ✓ | | |
| Saliva (1 collection) | | ✓ | ✓ | ✓ | | ✓ | | |

*Adapted from the HBCD Biospecimens Collection SOP*

# HBCD Study Preliminary* Biospecimen Results



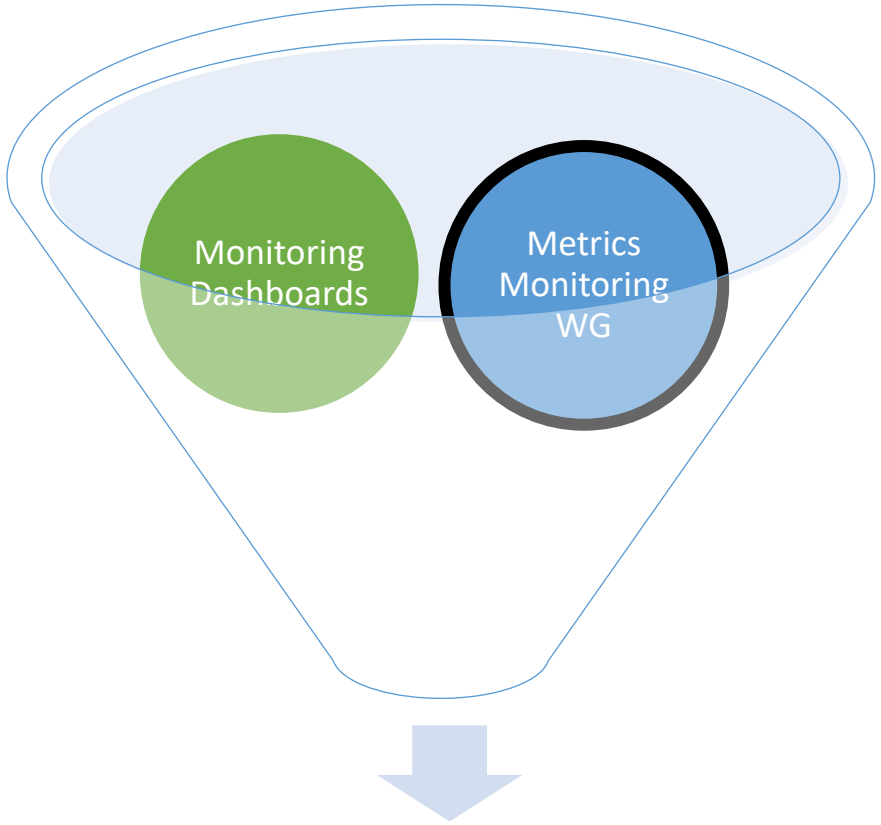

| Visit 1 Urinalysis | Number of Positive# Specimens |
|---|---|
| Alcohol | 8 |
| Benzodiazepines | 1 |
| Barbiturates | 1 |
| Cannabinoids | 69 |
| Nicotine | 86 |
| Amphetamine | 10 |
| Cocaine | 3 |
| Buprenorphine | 10 |
| Fentanyl | 8 |
| Methadone | 11 |
| Oxycodone | 1 |
| Other Opioids | 6 |




*#Positive counts reflect participants with a positive result on initial plus one (or more) confirmatory tests. Select subset of positive specimen tests shown.*

**Results are preliminary as of 05/01/2024; subject to change.*

# Oversight of the HBCD Study: Results-Based Accountability (RBA) Approach



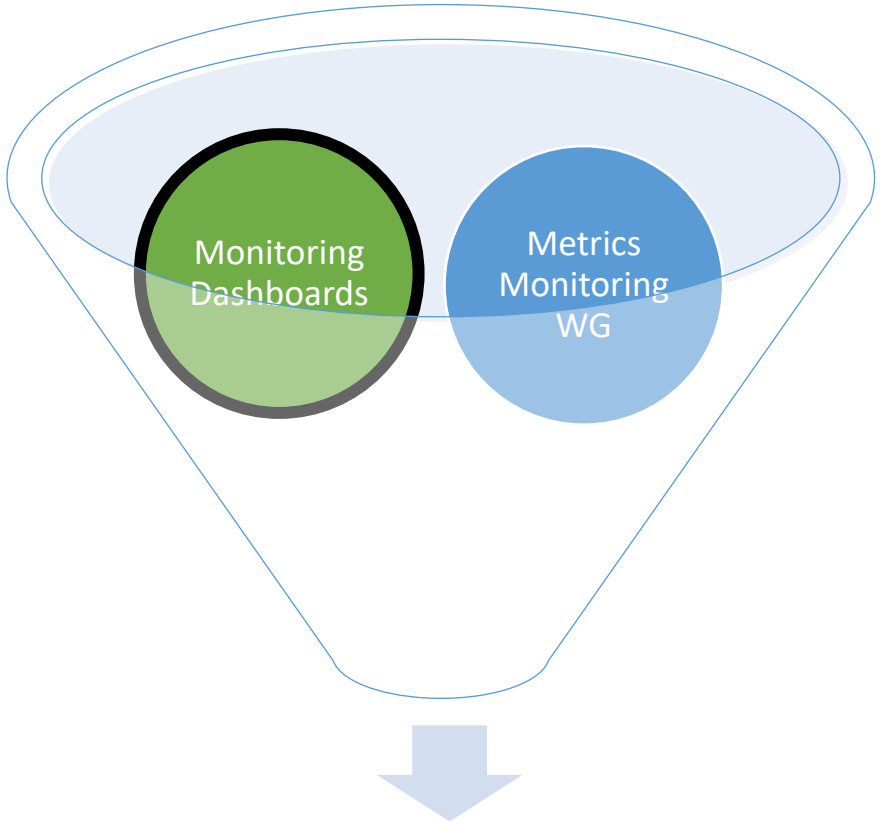

NIH NOA Expectations

Brenda Jones Harden, Ph.D.
Associate Director for Recruitment & Retention
MPI, U of Maryland site

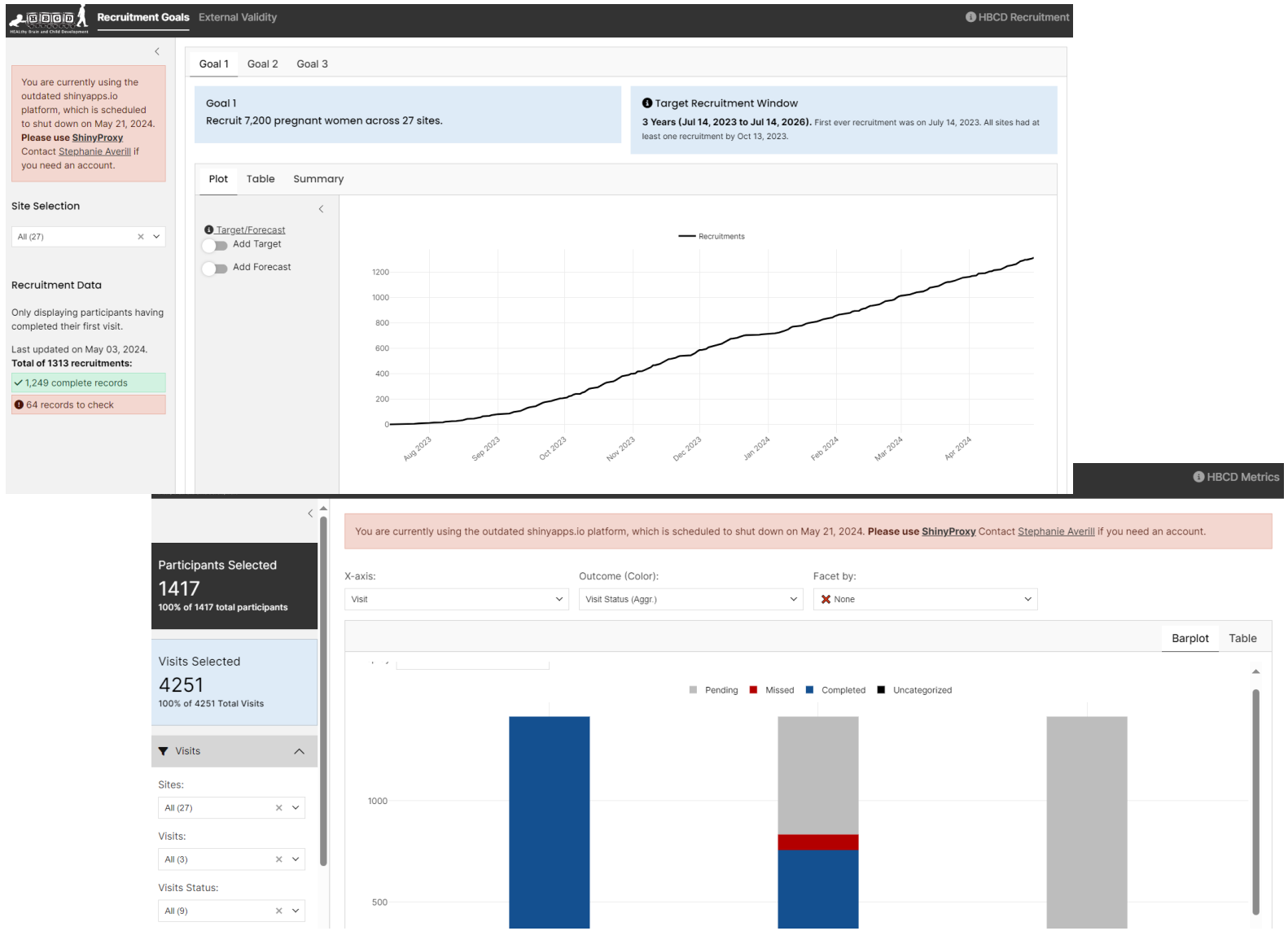
Terry Jernigan, Ph.D.
Co-Chair, RBA and metrics monitoring
Co-I, HBCD Coordinating Administrative Center

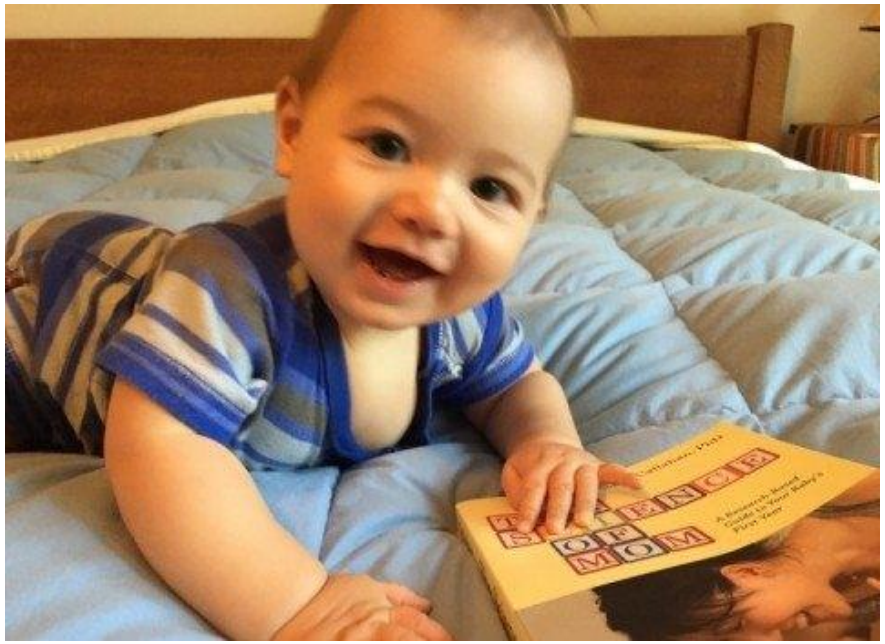
Keri Althoff, Ph.D.
Co-chair, metrics monitoring
Co-I, Johns Hopkins U site

# HBCD's Results-Based Accountability (RBA) Approach



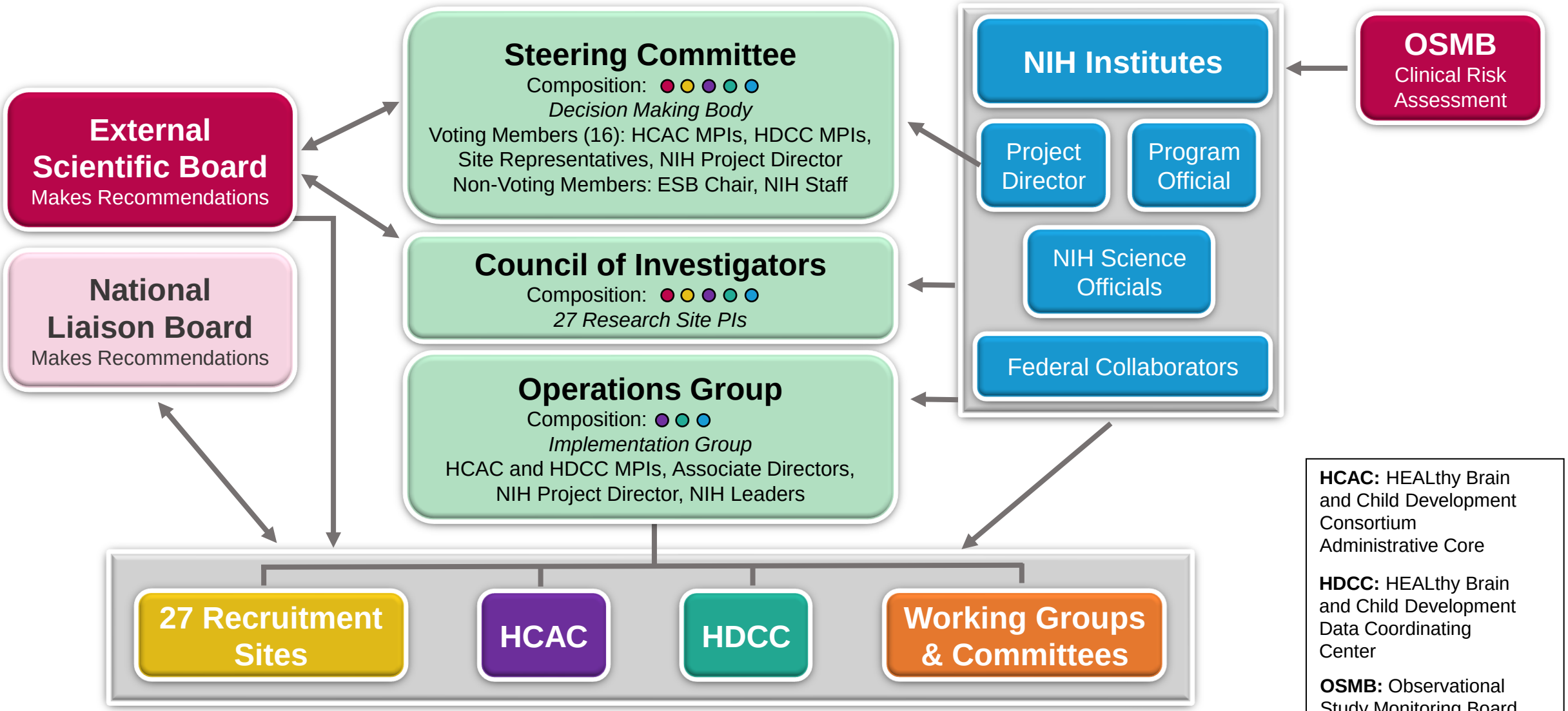

NIH NOA Expectations






# Questions?

# HBCD Leadership Structure



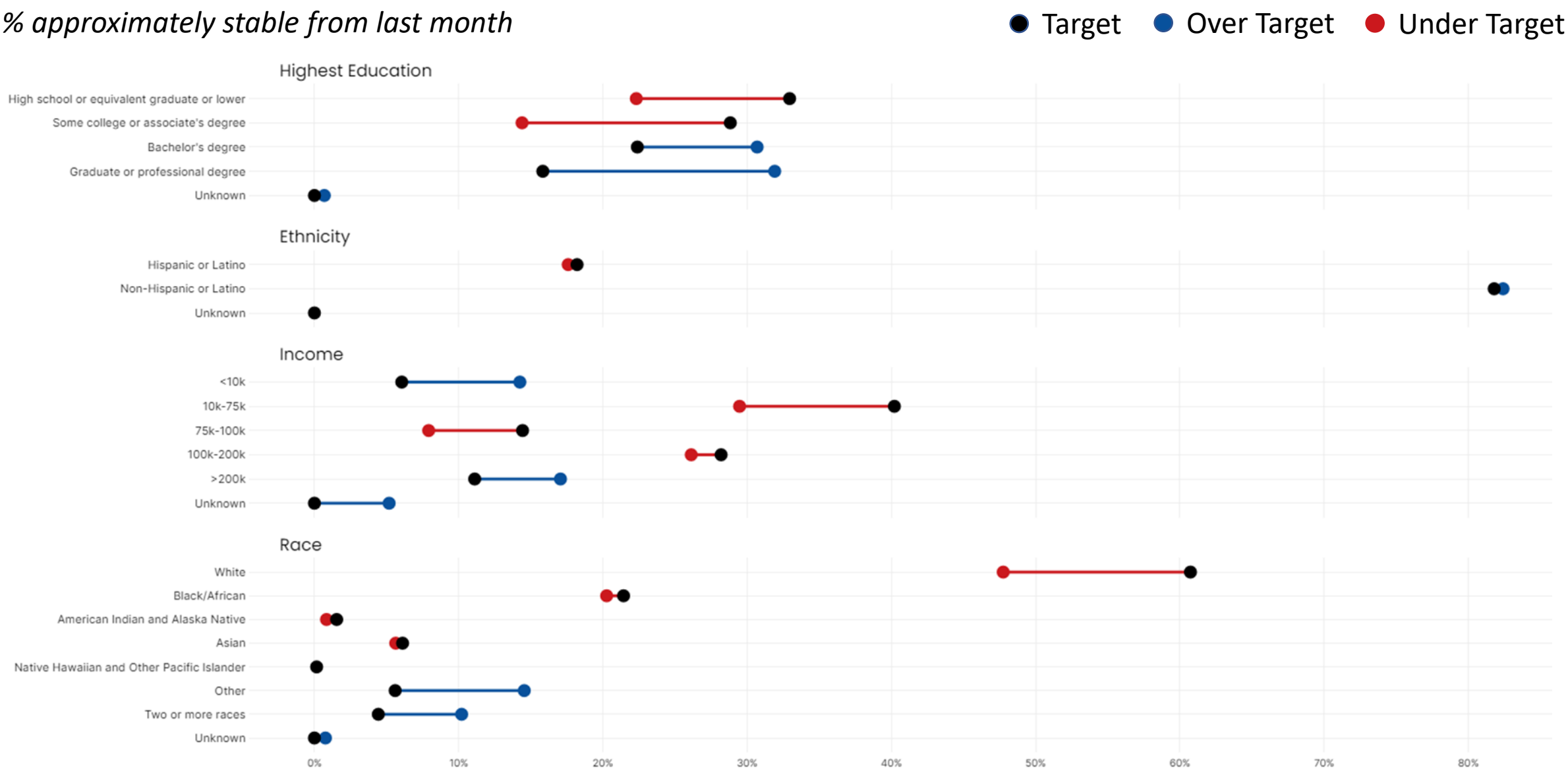

**HCAC:** HEALthy Brain and Child Development Consortium Administrative Core

**HDCC:** HEALthy Brain and Child Development Data Coordinating Center

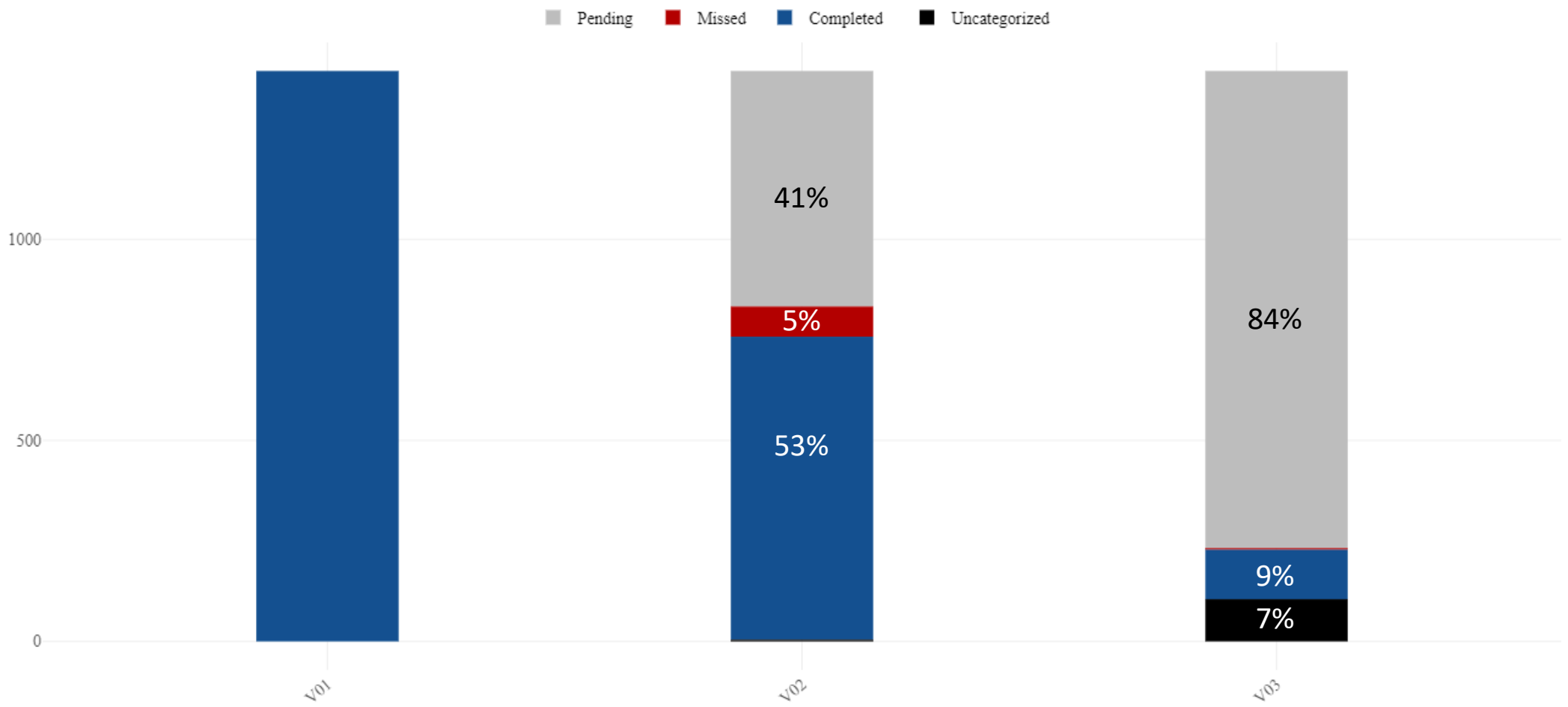
**OSMB:** Observational Study Monitoring Board

# HBCD Main Study External Validity

*% approximately stable from last month*



# HBCD Visit Status



# HBCD Study Biospecimens in Storage*

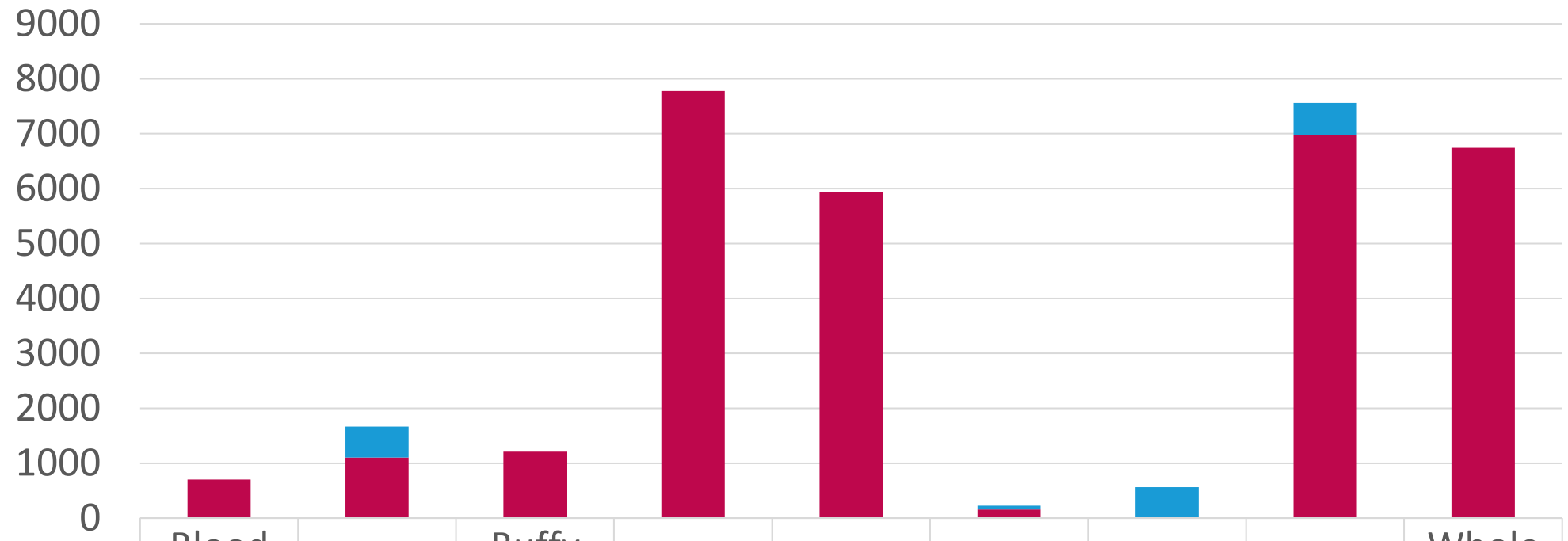
**Per Participant:**

Blood Aliquots

- Buffy coat: 1
- Plasma: 11
- Serum: 10
- Whole Blood: 12

Urine Aliquots

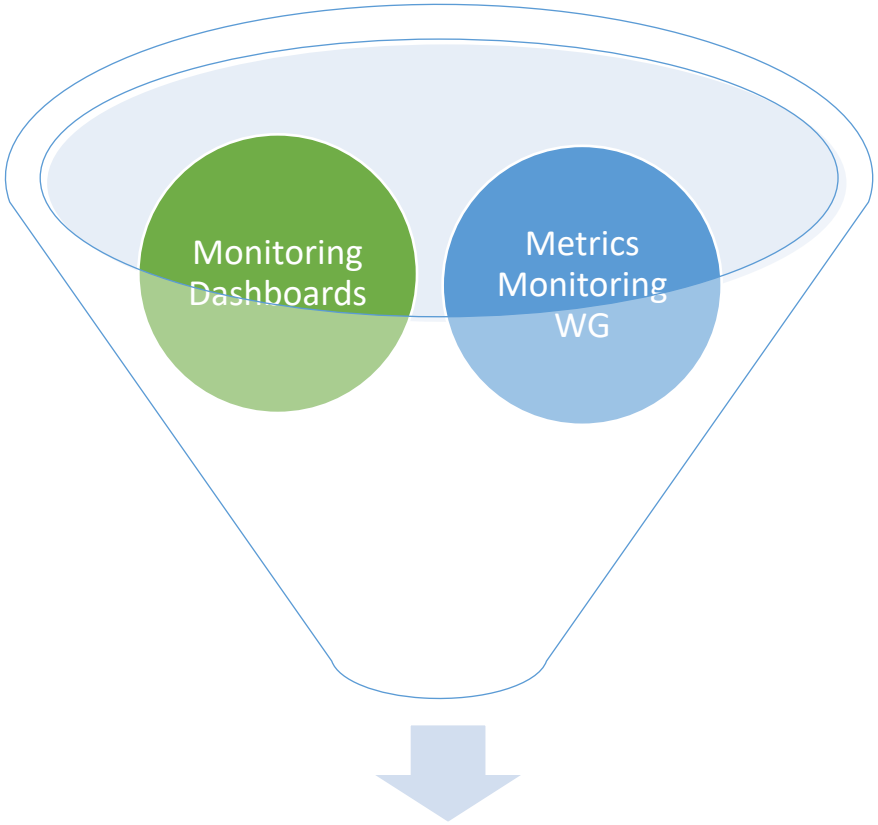
- Birth Parent: 11
- Child: 3




| | Blood Spot Cards | DNA-Saliva | Buffy Coat Aliquots | Plasma Aliquots | Serum Aliquots | Saliva | Stool | Urine Aliquots | Whole Blood Aliquots |
|---|---|---|---|---|---|---|---|---|---|
| Child (n=1,780) | | 566 | | | | 66 | 566 | 582 | |
| Birth Parent (n=30,606) | 703 | 1102 | 1210 | 7778 | 5934 | 160 | | 6977 | 6742 |

**Specimens in Storage as of 05/01/2024.*

# Oversight of the HBCD Study: Results-Based Accountability (RBA) Approach




NIH NOA Expectations

# Current Study Design

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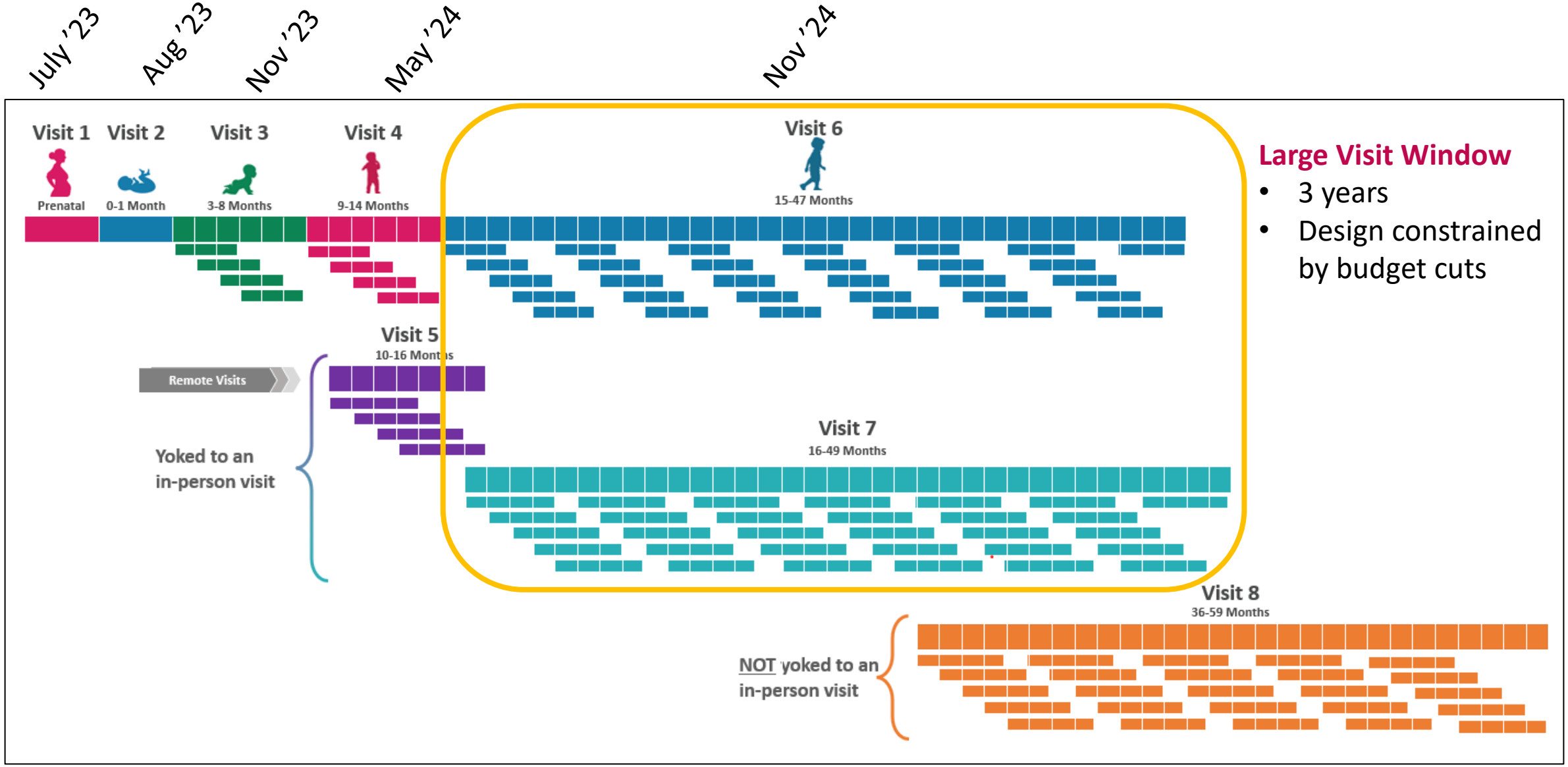


**Large Visit Window**

- 3 years
- Design constrained by budget cuts

# Justification for an Additional In-Person Visit

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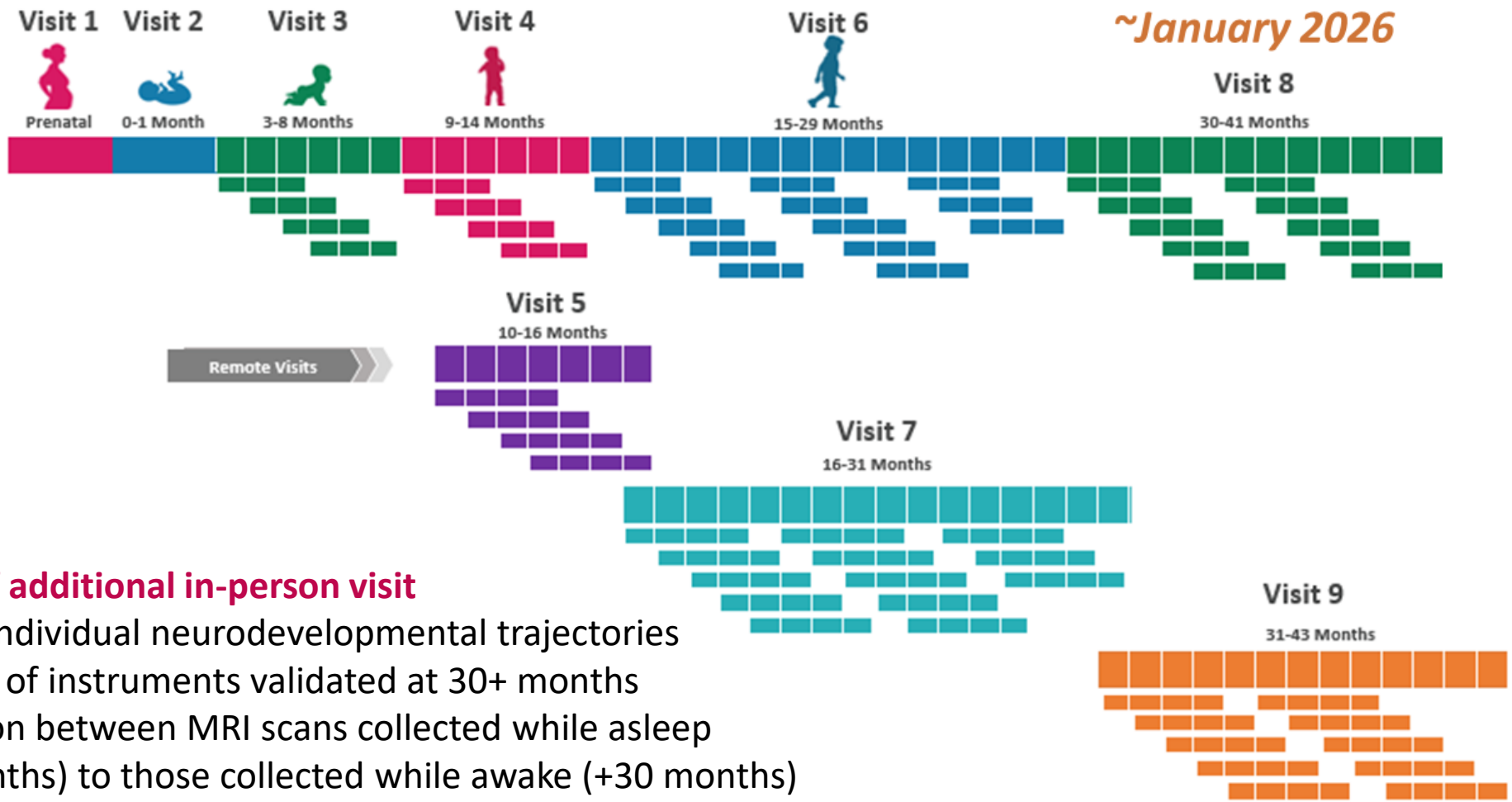


**BENEFITS of additional in-person visit**

- Refined individual neurodevelopmental trajectories
- Inclusion of instruments validated at 30+ months
- Separation between MRI scans collected while asleep (<30 months) to those collected while awake (+30 months)
- Maintain regular contact and engagement with participants

# Neurodevelopmental Trajectories

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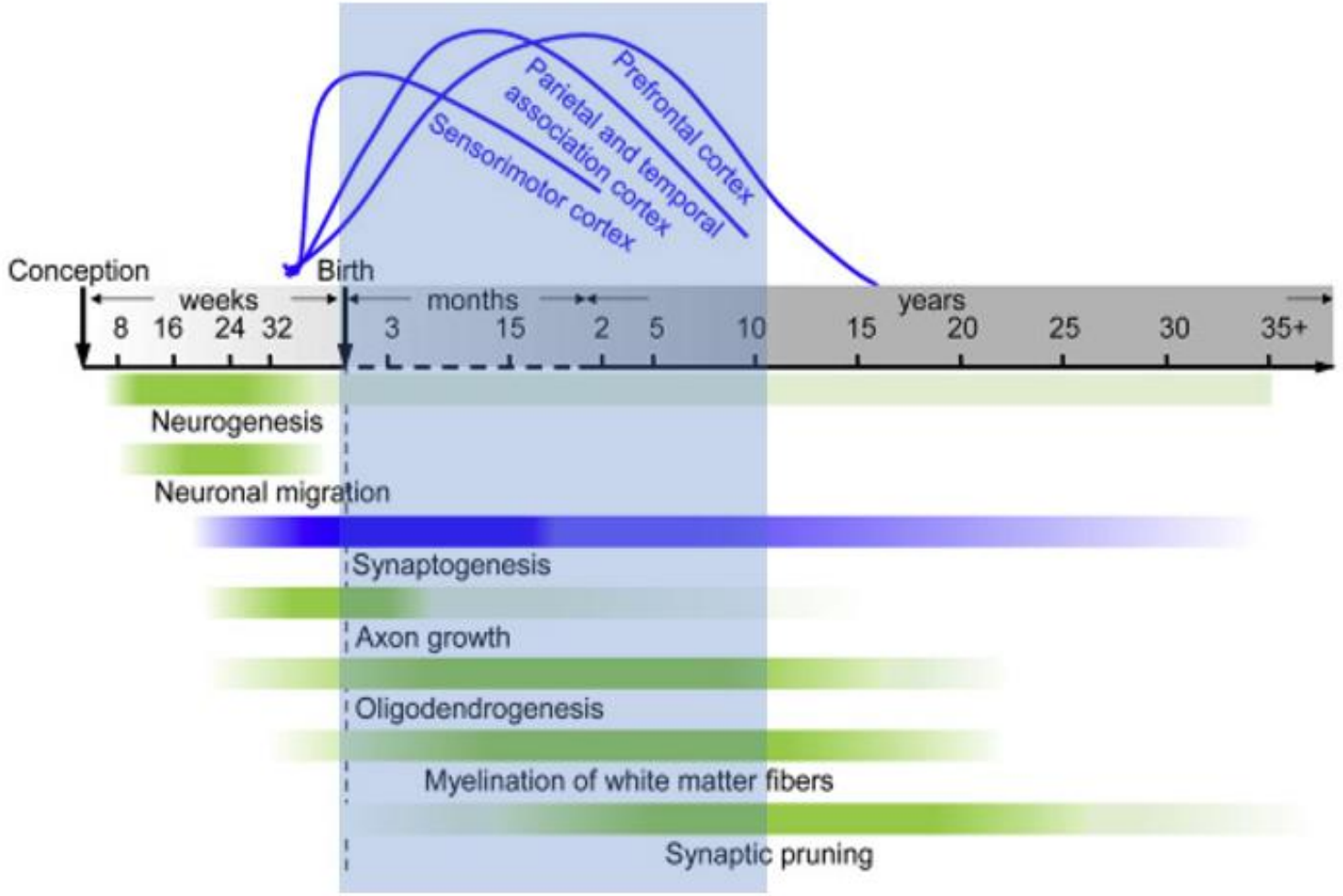


Ouyang et al., 2019 *NeuroImage*

# Trajectory Simulations from Biostats WG

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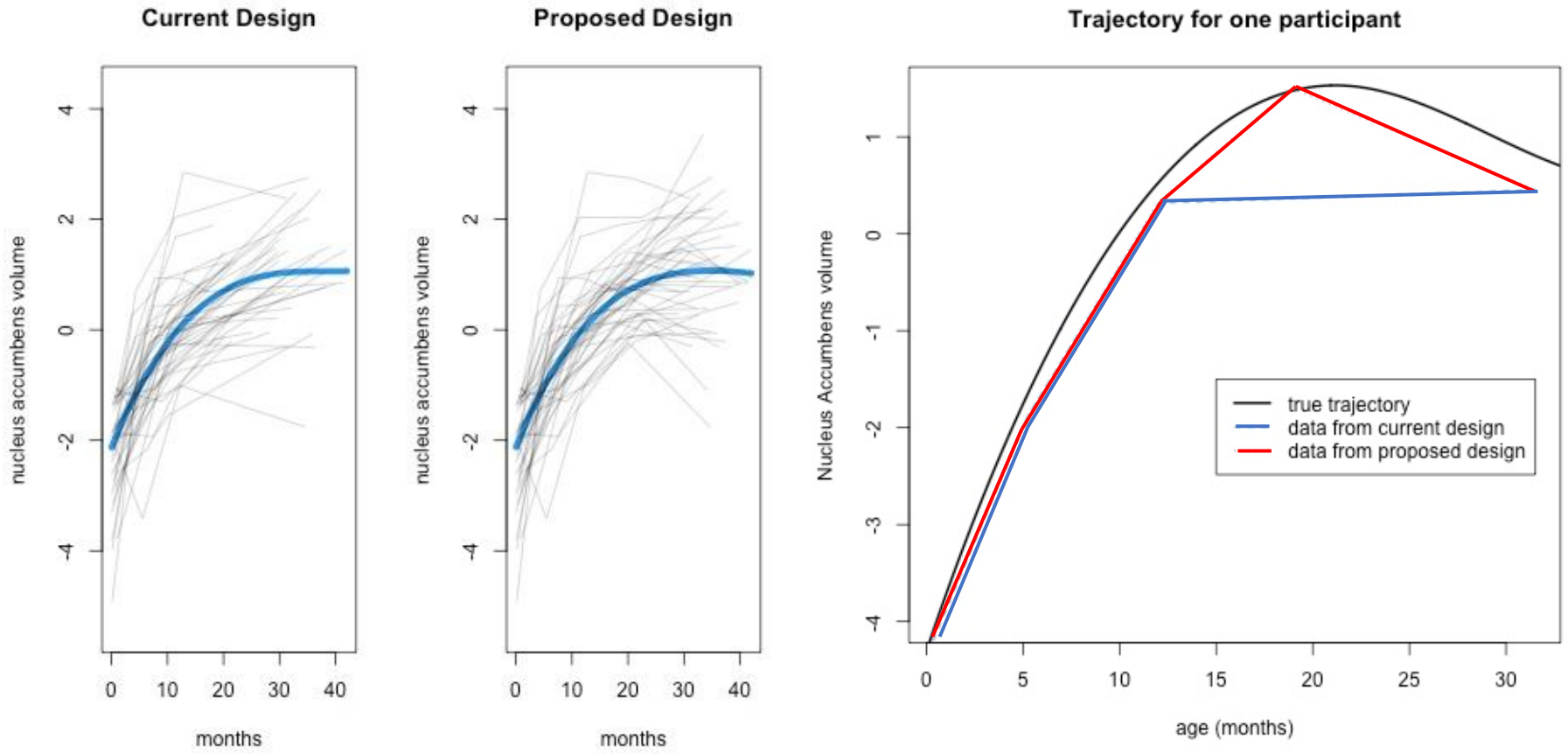
- Simulated data from the current and proposed HBCD visit designs.
- Realistic simulation settings were obtained from the Baby Connectome Project nucleus accumbens volume trajectories.
- Both designs can obtain good estimates of mean trajectories.
- **The addition of a visit in the 15–29-month range better captures individual variation in trajectories in this age range.**



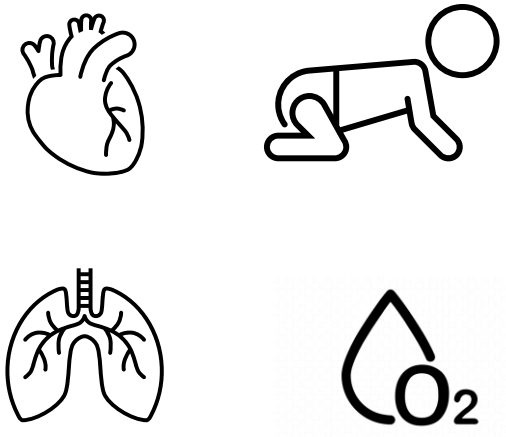
# Wearable Sensor Data Collection

**During V2 and V3**

- For 72 hours, child wears two **movement sensors on legs** and an **arm band sensor** that detects heart rate, $O_2$ saturation and respiration rate
- Parents fill in daily reports of infant behavior during this 72-hour period.

## Variables we can derive from sensors and their value as indices of health

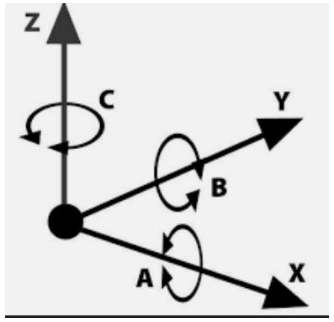
- Sleep/wake cycles and sleep state
- Amount and intensity of physical activity
- Patterns of movements across days
- Patterns of Autonomic Nervous System Functioning

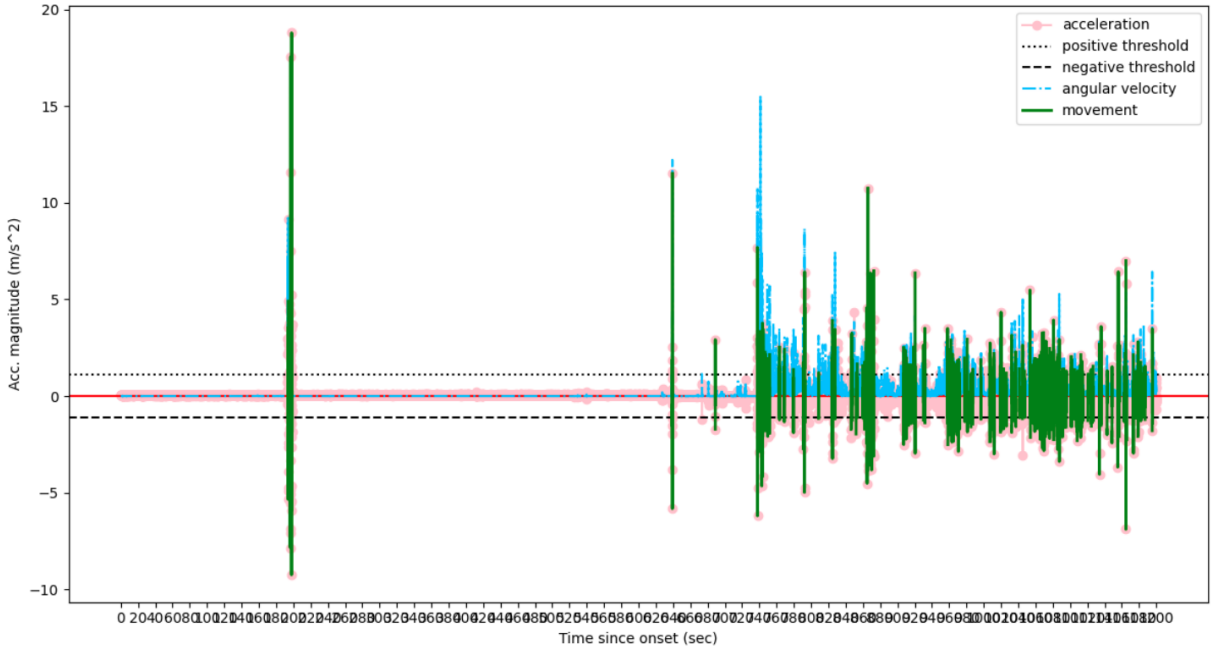


# Movement Sensor Data Analysis

**Axivity AX6 sensors**

- Measure 3 axes of accelerometer data and 3 axes of gyroscope data at 20 samples per second
- Accelerometer = acceleration = rate of change of velocity
  - 0 acceleration = not moving or moving at constant velocity
- Gyroscope = angular velocity = rate of rotation

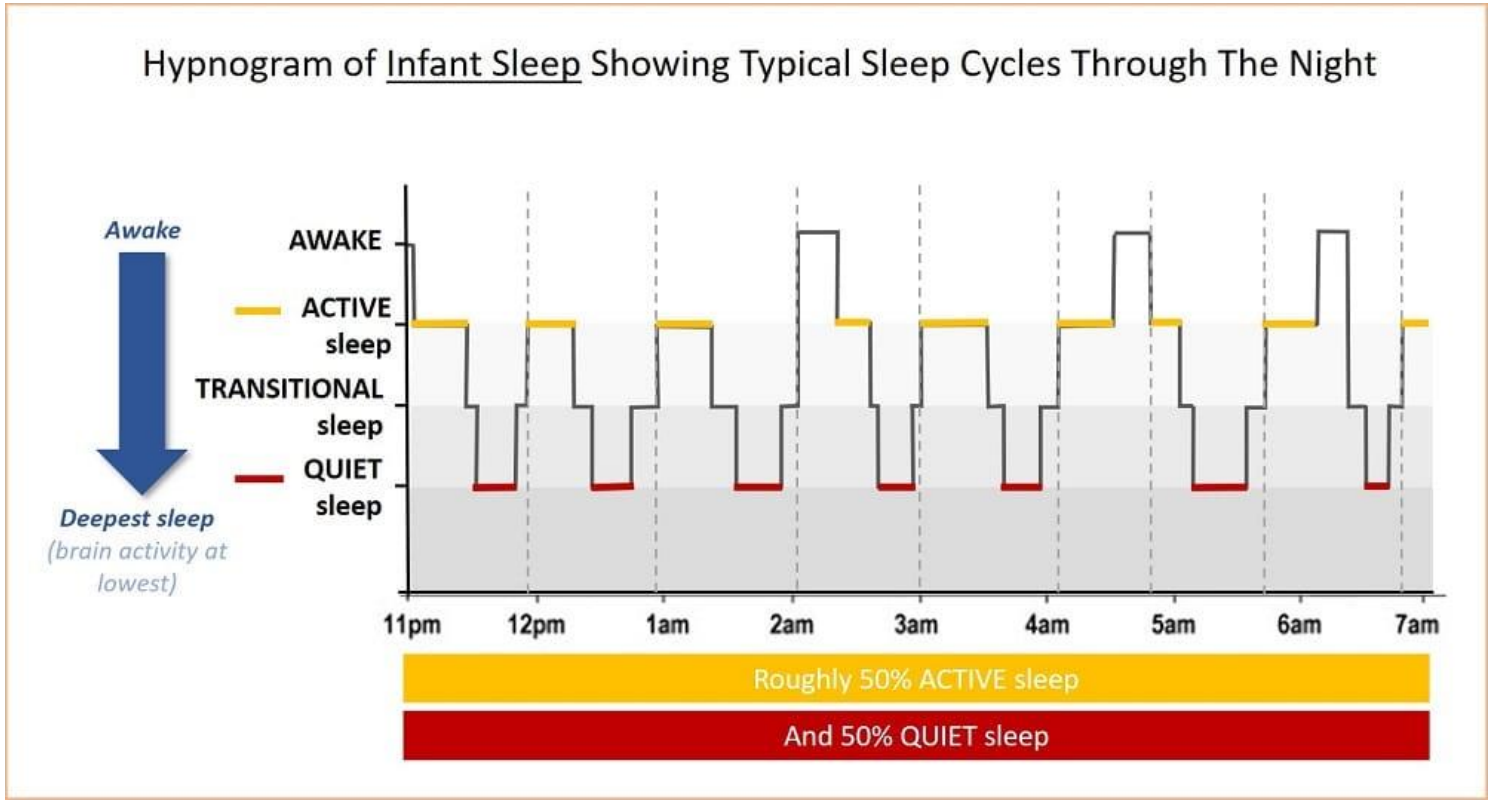



| Calculated Data | | |
|---|---|---|
| Total movements counted | Movement per hour awake (movement/ hour) | **Estimated sleep time (hours)** |
| Duration of movement (seconds) | Average acceleration per movement (m/s^2) | Peak acceleration per movement (m/s^2) |

# Arm Band Sensor Data Analysis

- Arm band data can be used to calculate sleep staging based on pulse rate and respiration rate




- Measures 3 signals:
  - Pulse Rate
  - Respiratory Rate
  - $O_2$ Blood Oxygen Saturation

Pini, N., Ong, J. L., Yilmaz, G., Chee, N. I., Siting, Z., Awasthi, A., ... & Lucchini, M. (2022). An automated heart rate-based algorithm for sleep stage classification: Validation using conventional polysomnography and an innovative wearable electrocardiogram device. *Frontiers in Neuroscience*, *16*, 974192.