The Precision Medicine Initiative® Cohort Program

Josephine Briggs, MD
Interim Director, NIH PMI Cohort Program

Gwynne Jenkins, PhD, MPH
Executive Secretary, NIH PMI Cohort Program Advisory Panel

The challenges …

- Many diseases lack effective prevention strategies, diagnostics, or treatments
  - Options fail to consider key differences among individuals: genes, lifestyle, environment
- Participants in biomedical research often treated as "subjects," not partners
- Research findings take too long to be implemented into clinical practice
- Need to look beyond the genome

State of the Union Address
January 20, 2015

FY16 NIH PMI Appropriation

• ***PMI Cohort Program*** • ***PMI for Oncology***	**$130 million** **$70 million**
TOTAL	$200 million

Other agencies part of President's PMI too:

- FDA
- ONC
- OCR
- etc.

Precision Medicine Initiative®: The Time Is Now

	Ten Years Ago	Now – 2014 (most recent data)
Cost of sequencing a human genome	$22,000,000	$1000 - $5000
Amount of Time to Sequence a Human Genome	2 years	<1 day
Number of smart phones in the United States	1 million (<2%)	160 million (58%)
EHR Adoption (% hospitals)	20-30%	>90%
Computing Power	n	n x 16
Participant & Patient Engagement	Expectations continually rising	

PMI Core Values

1. Participation is **open** to interested individuals
2. Representing the **rich diversity** of America is essential
3. Participants are **partners** in all phases of the cohort program
4. Participants have **access to study information** and data about themselves
5. Data can be **accessed broadly** for research purposes
6. Adherence to the PMI **privacy principles** and forth-coming **security framework**
7. PMI is a **catalyst** for progressive research programs and policies

Advisory Committee to the NIH Director

Precision Medicine Initiative® Working Group

Co-Chairs:

Richard Lifton, MD, PhD, Yale University School of Medicine, New Haven, CT
Bray Patrick-Lake, MFS, Duke University, Durham, NC
Kathy Hudson, PhD, National Institutes of Health, Bethesda, MD

Members:

- **Esteban Gonzalez Burchard, MD, MPH**
  University of California, San Francisco
- **Tony Coles, MD, MPH**
  Yumanity Therapeutics, Cambridge, MA
- **Rory Collins, FMedSci**
  University of Oxford, UK
- **Andrew Conrad, PhD**
  Google X, Mountain View, CA
- **Josh Denny, MD**
  Vanderbilt University, Nashville, TN
- **Susan Desmond-Hellmann, MD, MPH**
  Gates Foundation, Seattle, WA
- **Eric Dishman**
  Intel, Santa Clara, CA
- **Kathy Giusti, MBA**
  Multiple Myeloma Res Foundation, Norwalk, CT
- **Sekar Kathiresan, MD**
  Harvard Medical School, Boston, MA
- **Sachin Kheterpal, MD, MBA**
  University of Michigan Medical School, Ann Arbor
- **Shiriki Kumanyika, PhD, MPH**
  U Penn Perelman School of Medicine, Philadelphia
- **Spero M. Manson, PhD**
  University of Colorado, Denver
- **P. Pearl O'Rourke, MD**
  Partners Health Care System, Inc., Boston, MA
- **Richard Platt, MD, MSc**
  Harvard Pilgrim Health Care Institute, Boston, MA
- **Jay Shendure, MD, PhD**
  University of Washington, Seattle
- **Sue Siegel**
  GE Ventures & Healthymagination, Menlo Park, CA

Charge to the PMI Working Group of the ACD

To develop a vision for the PMI Cohort Program and advise on the design of a longitudinal national research cohort of ≥1 million volunteers

- Leverage existing cohorts, start from scratch, or hybrid?
- How to capture the rich diversity in the U.S. population?
- What data types should be included?
- What policies need to be in place for maximal benefit?

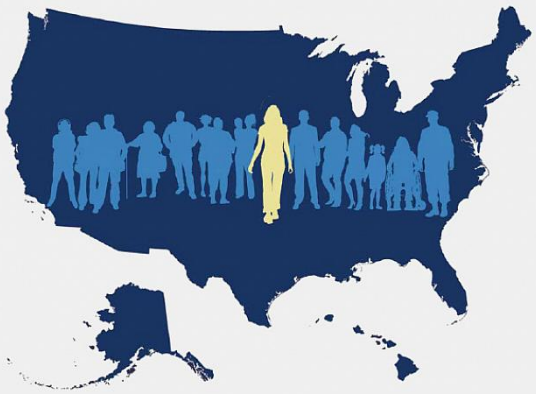
Inputs

- Workshops
  - Unique Scientific Opportunities for the National Research Cohort (April 28-29, NIH, Bethesda, MD)
  - Digital Health Data in a Million-Person Precision Medicine Initiative (May 28-29, Vanderbilt University, Nashville, TN)
  - Participant Engagement and Health Equity (July 1-2, NIH, Bethesda, MD)
  - Mobile and Personal Technologies in Precision Medicine (July 27-28, Intel Corp., Santa Clara, CA)
- Requests for Information
  - Building the cohort
  - Strategies to address community engagement and health disparities
- FNIH Survey of public perceptions of precision medicine cohort
- White House Privacy and Trust Principles

FNIH Survey of public opinion on a large US cohort study

- 79% agree cohort probably/definitely should be done
- 54% would probably/definitely participate in the cohort
- What motivates participation?
  - 82% interested in receiving results of study
  - 62% wish to help advance health research
- 71% said participants should be partners with researchers

ACD PMI Working Group Report
September 17, 2015



The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine

Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH

September 17, 2015

Scientific Opportunities in the PMI Cohort Program

- Develop quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors and gene-environment interactions
- Identify the causes of individual variation in response to commonly used therapeutics (pharmacogenomics)
- Discover biological markers that signal increased or decreased risk of developing common diseases
- Use mobile health (mHealth) technologies to correlate activity, physiological measures and environmental exposures with health outcomes
- Develop new disease classifications and relationships
- Empower study participants with data and information to improve their own health
- Create a platform to enable trials of targeted therapies

Recommendations for assembling the PMI Cohort

- **One million or more** U.S. volunteers
  - Broadly reflect the diversity of America (including family members of all ages, health statuses, areas)
  - Strong focus on underrepresented groups
- **Longitudinal cohort**, with continuing interactions, recontactable for secondary studies
  - Collect EHR data, provide biospecimen(s) and survey, and complete a baseline exam
- Two methods of **enrollment**
  - Direct volunteers: anyone can sign up
  - Healthcare provider organizations (incl. FQHCs): diverse participants, robust EHRs, participant follow-up
- Substantial **participant engagement** in development, implementation, governance

Benefits of Approach

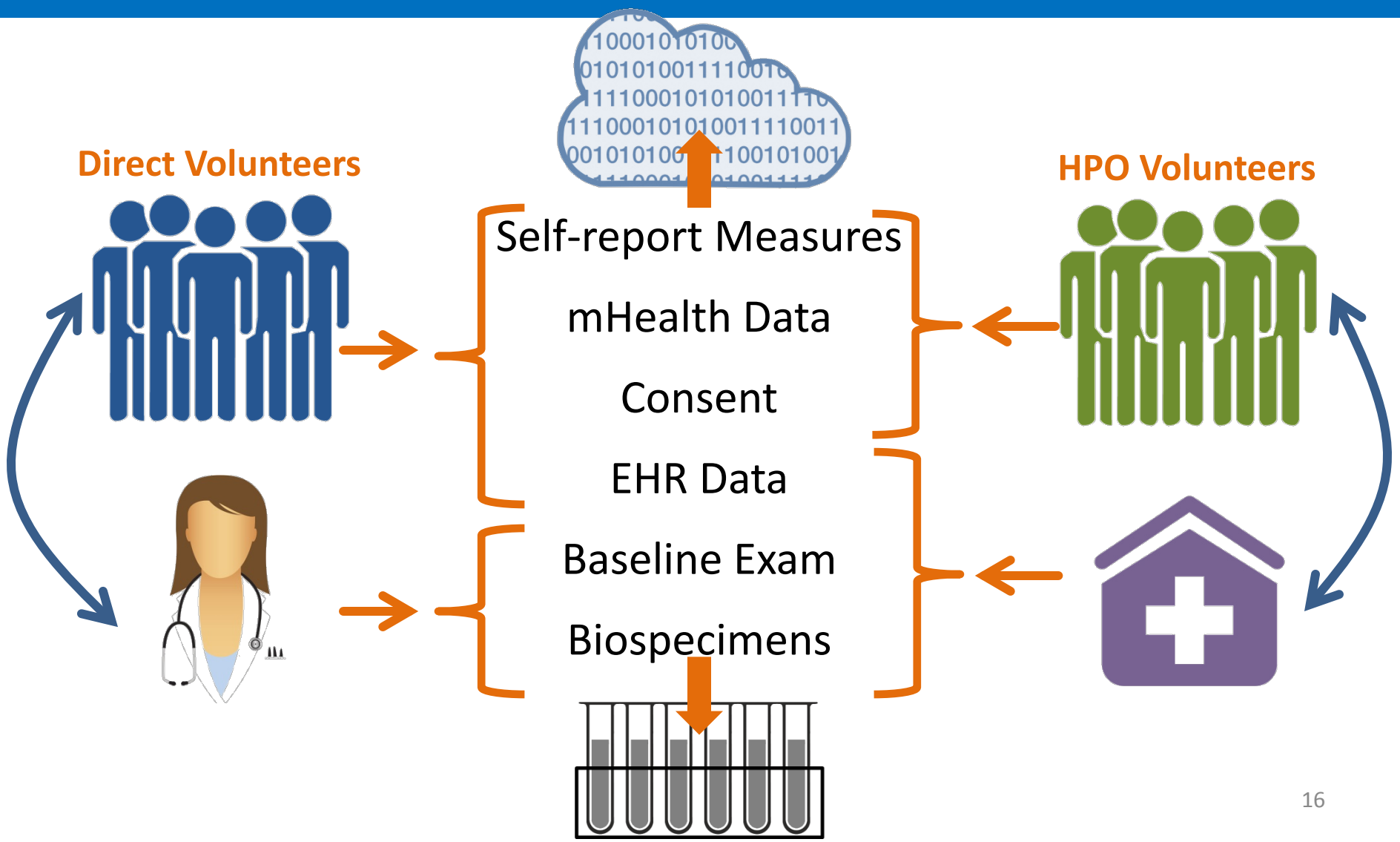
- Large and diverse
  - Less costly and less difficult than representative sample (which is rarely achievable)
  - Able to generate estimates of effect/association
  - Permits well-powered samples
- Support focus on underserved and underrepresented populations
- Prospectively understand resistance to & development of diseases
- Complement (not duplicate) existing disease-specific cohorts

Initial Core Data Set

- Centrally collected and stored in a Coordinating Center
- Align with other data sets when possible
- Leverage existing data standards and common data models when possible

Data Source	Data Provided
Self report measures	Diet, substance use, self-report of disease and symptoms (e.g., cognitive or mood assessment)
Baseline health exam	Vitals (e.g., pulse, blood pressure, height, weight), medical history, physical exam
Structured clinical data (EHR)	ICD and CPT codes, medication history, select laboratory results, vitals, encounter records
Biospecimens	Blood sample
mHealth data	Passively-collected data (e.g., location, movement, social connections) from smartphones, wearable sensor data (activity, hours and quality of sleep, time sedentary).

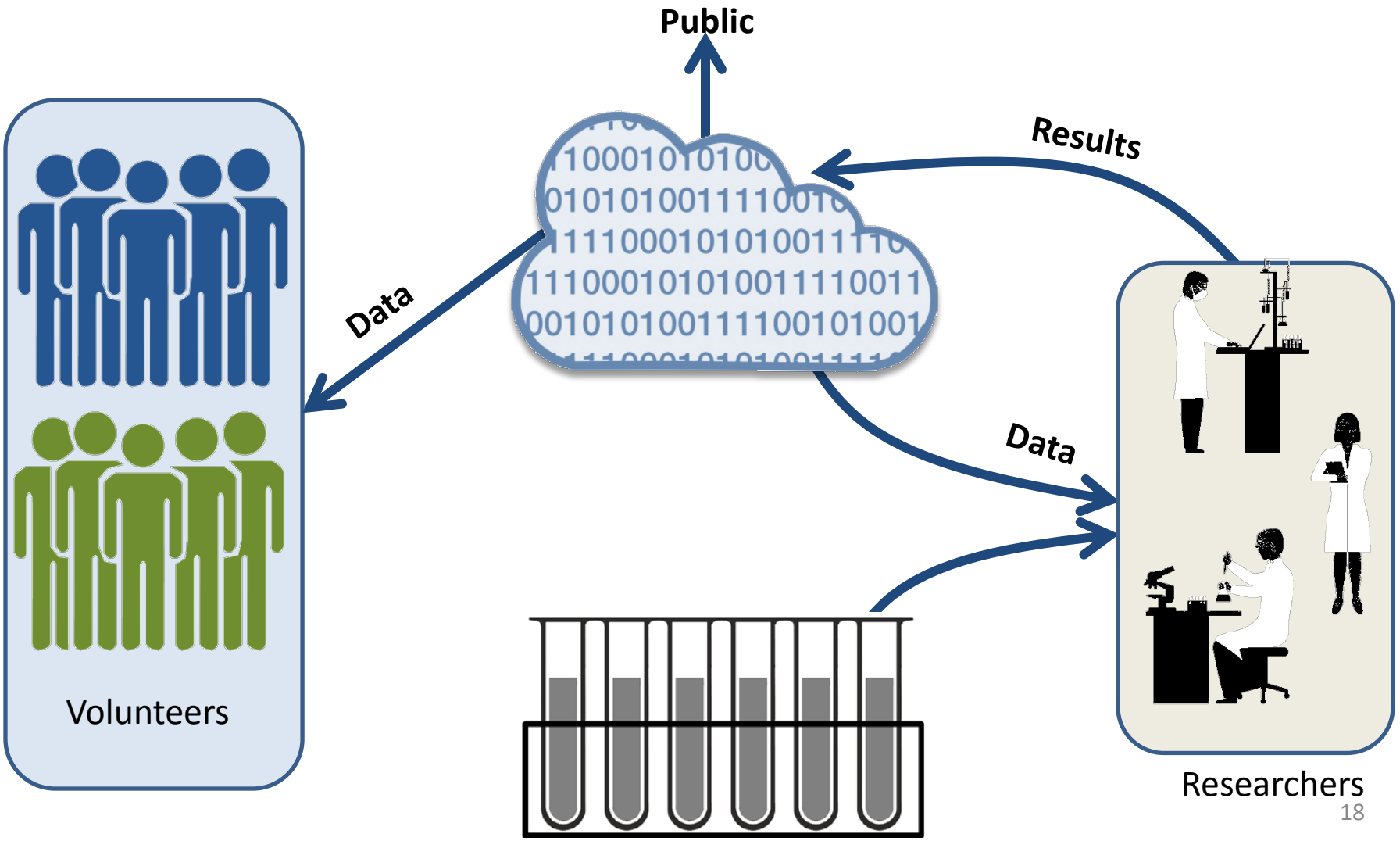
Information Flow In



Possible data sources for the PMI Cohort

Data Source	Example Data Provided
Self report measures	Diet, substance use, self-report of disease and symptoms (e.g., cognitive or mood assessment
Structured clinical data (EHR)	ICD and CPT codes, medication history, laboratory results, vitals, encounter records
Unstructured clinical data (EHR)	Narrative documents, images, EKG and EEG waveform data
Biospecimens	Blood sample, microbiome, nail and hair for environmental exposures over time
mHealth and sensor data	Passively-collected data (e.g., location, movement, social connections), wearable sensor data (activity, calories expended, hours and quality of sleep, time sedentary).
Healthcare claims data	Billing codes as received by public and private payors, outpatient pharmacy dispensing
Geospatial and environmental data	Weather, air quality, environmental pollutant levels, food deserts, walkability, population density, climate change
Other data	Social networking e.g., Twitter feeds, over-the-counter medication purchases

Information Flow Out



Return of Results and Data

- Participants may receive, depending on their preferences:
  - Individual data
  - Individual health information
  - Ongoing study updates
  - Aggregated results

Participant Engagement in the PMI Cohort Program

- Participant substantially represented at all junctures
  - Governance, incl. Return of Results, Data, Resource Access, Biobanking, Security
  - Design of cohort
  - Conduct of research
    - IRB
  - Dissemination of results
  - Evaluation of program
  - Build a strong foundation of trust
- Core requirement for participating entities
- Focus of launch phase

Policy for the PMI Cohort Program

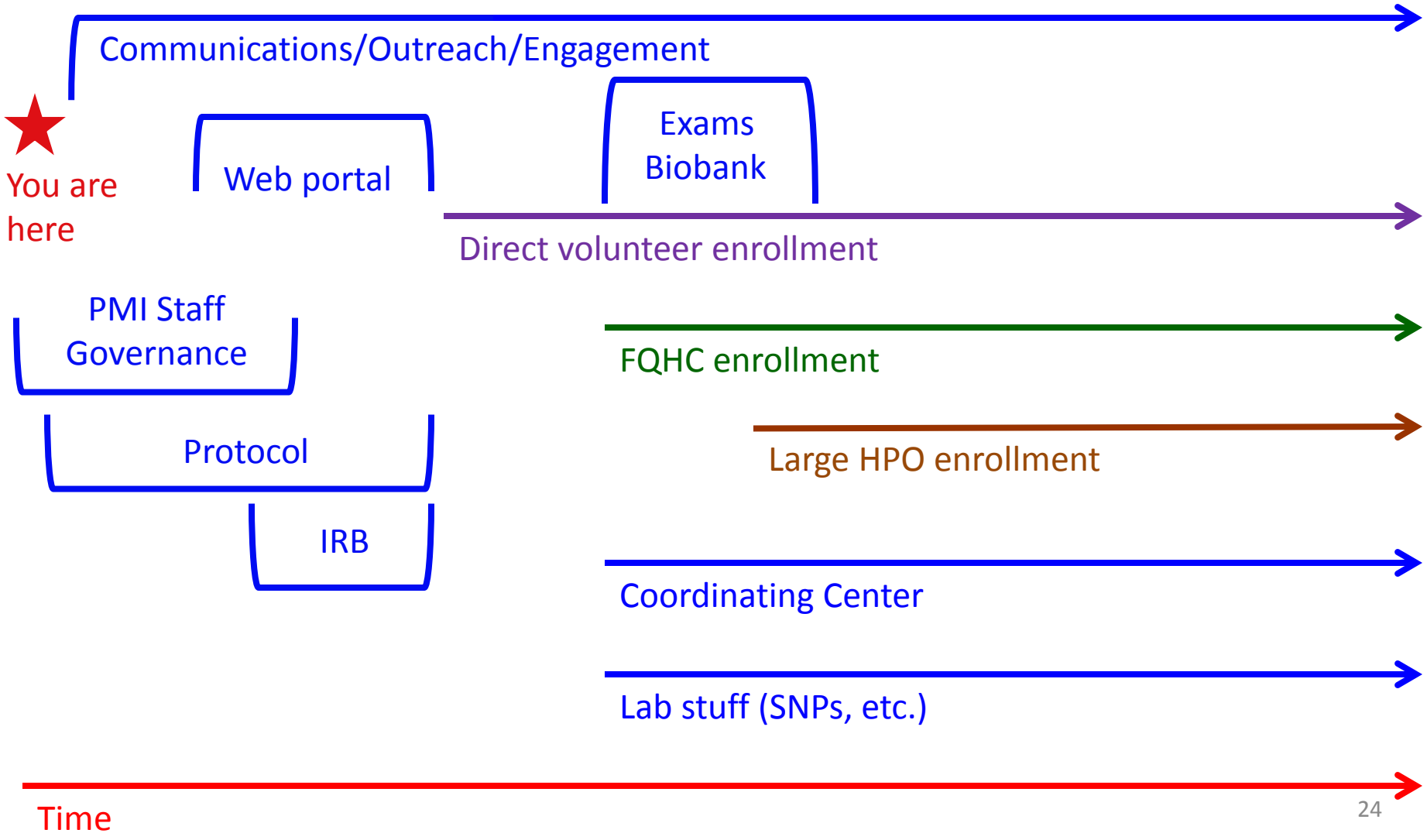
- Policy needs for PMI Cohort Program:
  - Single Institutional Review Board (IRB)
  - Privacy and security
    - Standards for data security
    - Safeguards against unintended data release
    - Penalties for unauthorized re-identification
  - Share results and provide access to data
    - Clarify CLIA and HIPAA
- Special policy considerations about enrollment/retention of:
  - children
  - decisionally impaired
  - participants who become incarcerated

PMI Cohort Program Governance

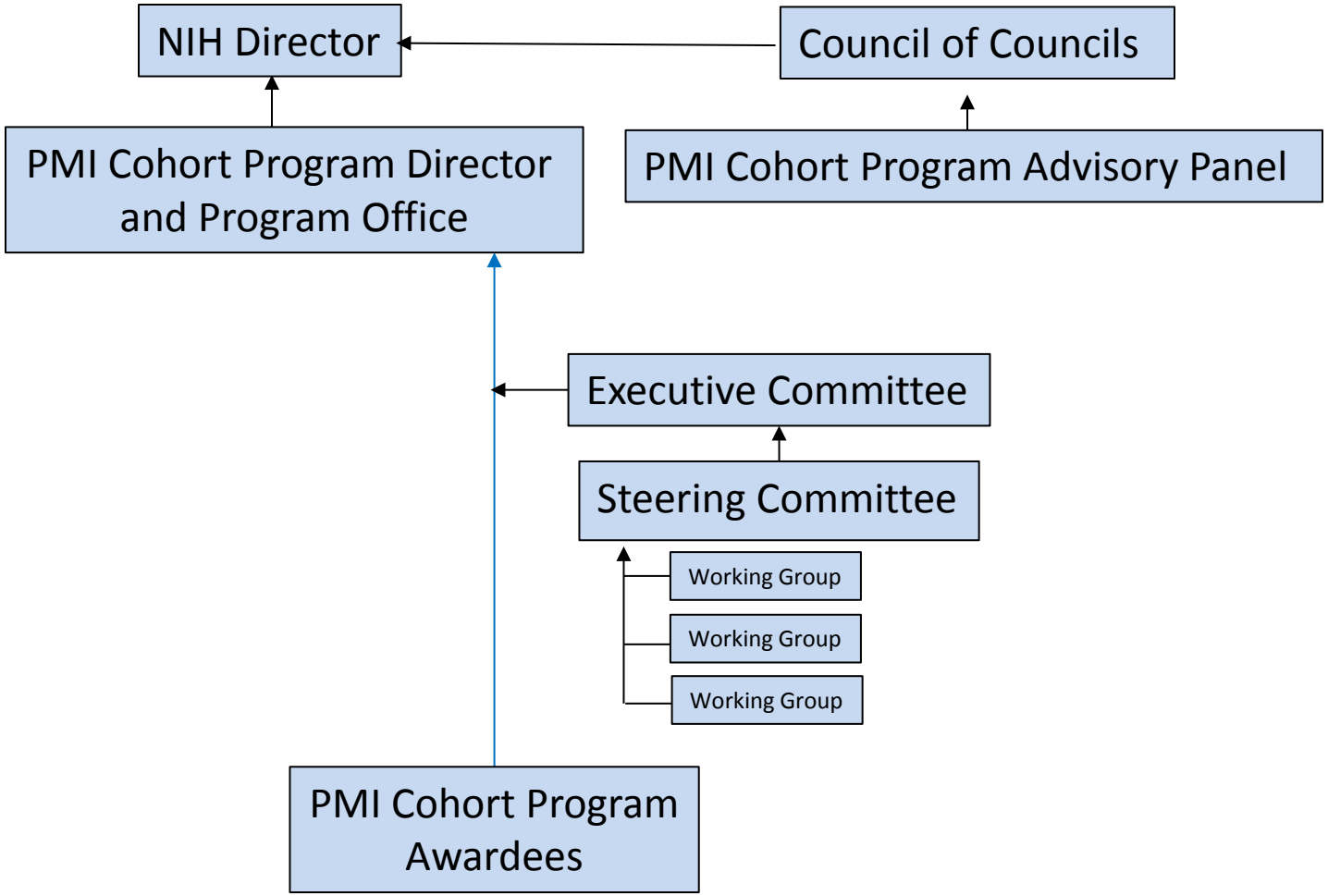
- Governance structure
  - PMI Cohort Program Director
  - PMI Cohort Program Advisory Panel
  - Executive Committee
  - Steering Committee with five subcommittees
    - Return of results and information
    - Data
    - Biobanking
    - Resource Access
    - Security
- Maintain interagency coordination

Former PMI Working Group Member Comments

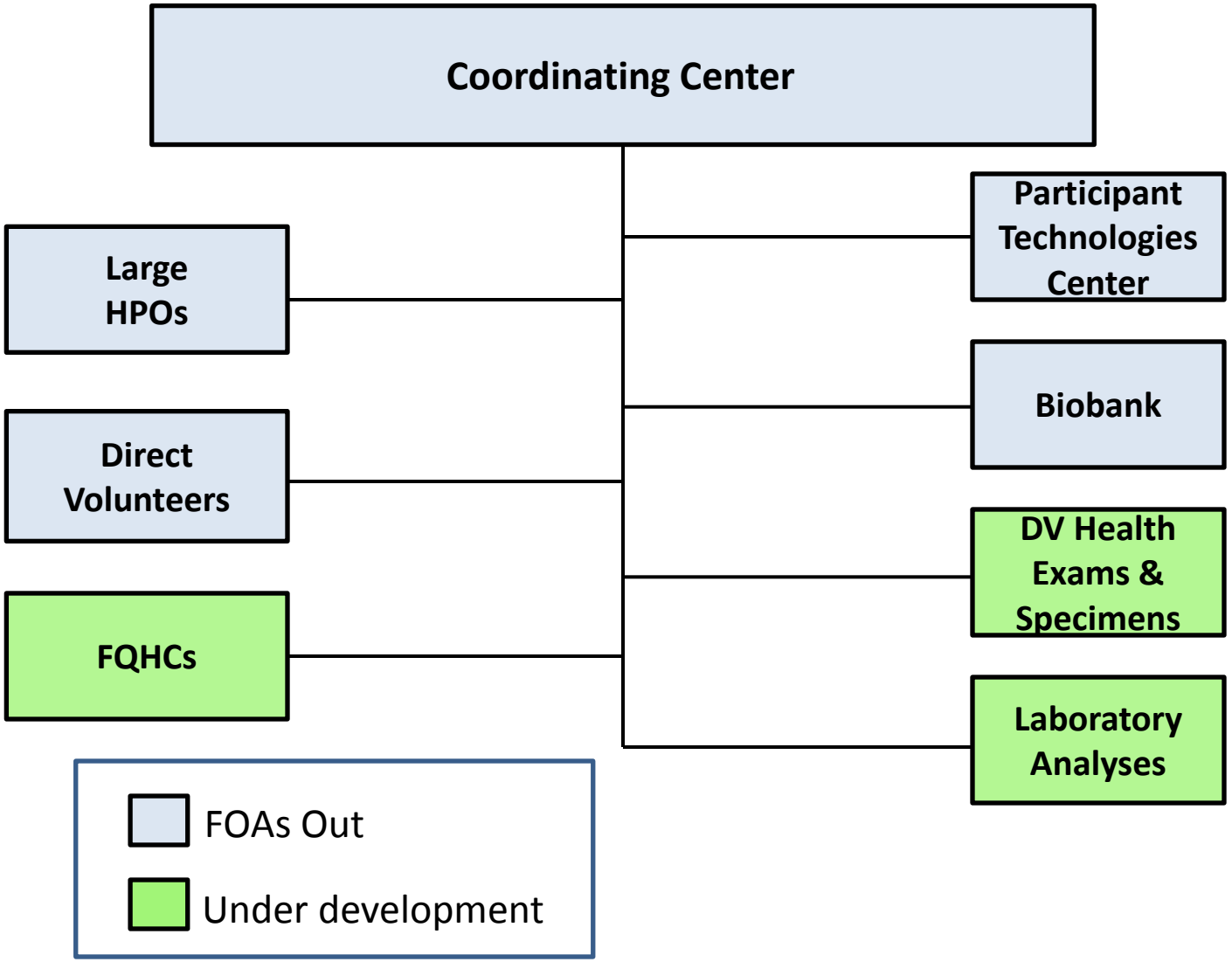
Initial Vision for Implementation



Governance


NIH Director
Council of Councils
PMI Cohort Program Director and Program Office
PMI Cohort Program Advisory Panel
Executive Committee
Steering Committee
Working Group
Working Group
Working Group
PMI Cohort Program Awardees

PMI Cohort Program



Projected Enrollments

	Estimated Cumulative Enrollments per Calendar Year			
Entry point to cohort	**2016**	**2017**	**2018**	**2019**
HPOs	28,000	196,000	448,000	595,000
Direct volunteers	50,000	150,000	252,000	352,000
FQHCs	<1,000	51,000	101,000	151,000
TOTALS	**~79,000**	**397,000**	**801,000**	**1,098,000**

Implementation Progress

January 2015	President launches Precision Medicine Initiative®
March 2015	NIH names ACD PMI Working Group
September 2015	ACD receives and approves PMI Working Group Report
November 2015	**6 funding opportunities issued**
December 2015	**PMI Cohort Program Advisory Panel convened**
January 2016	**Search for Director closed**
January 2016	**1st & 2nd level review for pilots**
February 2016	**Pilot awards made**

PMI Cohort Program Advisory Panel

Lon Cardon, Ph.D.
GlaxoSmithKline

Alta Charo, J.D.
University of Wisconsin

Tony Coles, M.D., M.P.H.
Yumanity Therapeutics

Rory Collins, FRS
University of Oxford

Eric Dishman
Intel

Alejandra Gepp, M.A.
National Council of La Raza

Sachin Kheterpal, M.D., M.B.A.
University of Michigan Medical School

Marie Lynn Miranda, Ph.D.
Rice University

Bray Patrick-Lake, M.F.S.
Duke University

Dara Richardson-Heron, M.D.
YWCA

Gregory Simon, M.D., M.P.H.
Group Health Research Institute

Sharon Terry, M.A.
Genetic Alliance

David Williams, Ph.D., M.P.H.
Harvard University

Coordinating Center: Administrative Core

- **Scientific & Administrative leadership**
  - Co-chair Steering and Executive Committees
  - Ensure effective transition from pilot phase
  - Coordinate core protocol development
  - Monitor enrollment, retention, and protocol implementation from both DV and HPO participants
- **Direct Volunteer Operations**
  - Point-of-contact for direct volunteers
  - Schedule & track biospecimens and physical evaluations
- **Healthcare Provider Organization (HPO)-related Operations**
  - Ensure effective protocol implementation and consistent patient engagement strategies

Coordinating Center: Data Core

- **General functions**
  - Develop & maintain all shared scientific and management data
  - Develop and oversee implementation of a common data model
  - Establish standards and implement processes for federated data
  - Establish and implement standards for RUID, consent preferences, self-report, clinical & biospecimen data, return of results
  - Oversee all aspects of data security
  - Oversee all aspects of participant privacy protection
- **Health IT Specific Operations**
  - Provide effective interfaces that facilitate integration of data from health IT records both from HPOs and from DV (Blue Button) records

Coordinating Center: Research Support Core

- Establish and oversee secure computing environment
- Define analytical capabilities for data core
- Develop software tools & algorithms for datasets
- Provide all needed researcher-focused services
- PoC for all users at all levels of sophistication to design and implement studies using the PMI Cohort Program datasets and technical issues
- Provide interface to future –omics lab services
- Oversee the development, analysis and quality assessment of cohort-wide lab analysis

Healthcare Provider Organization Enrollment Centers (UG3/UH3)

- Establish structures to enroll participants, including family members and meeting diversity targets
- Establish effective local participant engagement, monitor participant enrollment and retention:
  - UG3: >10K expected enrollees
  - UH3: >35K expected enrollees/yr
- Conduct baseline physical evaluation on all enrolled participants
- Collect baseline biospecimens on all enrolled participants; legacy biospecimens will not be used
- Establish methods to capture complete health care information of all enrolled participants, both ongoing and when possible legacy data
- Develop methods to transmit health care information to CC in standardized format, meeting interoperability standards across the consortium
  - Standards for EHR capture and representation of family health history
  - SNOMED CT and HL7 Version 3

Participant Technologies Center (U24)

- Develop, upgrade mobile applications developed in pilot phase for DV enrollment, supporting their use for entire cohort
- Provide parallel platforms for non-smartphone users (e.g., feature phones, web site)
- Provide scientific leadership and technical expertise for use of mHEALTH technologies across the cohort
  - Develop, pilot and implement use across the cohort of data acquisition from a wide array of potential participant technologies,
  - Devices should include participants own devices, novel sensors and wearable devices
- Test emerging technologies for study deployment, validate, and co-calibrate emerging technologies with existing technologies to ensure continuity of trend data over time

Biobank (U24)

- Provide biospecimen collection kits and mailers
- Receive, process, store, and distribute:
  - Phase 1: receive saliva or blood
  - Phase 2: plasma, serum, RBCs, buffy coats, urine, DNA
- Establish automation of specimen aliquoting, DNA extraction initially; Transition to automated specimen retrieval systems, when it is cost effective
- Set up information systems for sample tracking, coordinating RUIDs with CC as well as other PMI Cohort Program sites
- Establish robust QA and QC, CLIA processes

Direct Volunteers Specimen Collection and Physical Evaluation

- It will be essential to develop an effective strategy to provide the simple physical evaluation and biospecimen collection from volunteers living anywhere in the US
- Partnerships with a variety of organizations are possible
- NIH issued RFI (NOT-OD-15-107) asking for input on how to achieve this part of the program cost effectively

Direct Volunteers Pilot Studies (OT)

- Develop and test innovative methods and technologies for data collection and management, and participant engagement
  - Website to engage potential volunteers
  - Participant interface optimized to keep participants engaged and return information
  - Pilot expansion of recruitment to family members
  - Data structures ensure the secure collection and sharing
  - Approaches for biospecimen collection

Communication Support (OT)

- Support communication efforts for the PMI research programs at NIH, with particular emphasis on the PMI Cohort Program
  - Communications planning, message and visual identity development
  - Collection and analysis of evaluation metrics.
  - Outreach through a variety of strategies and platforms

Other Transaction Authority

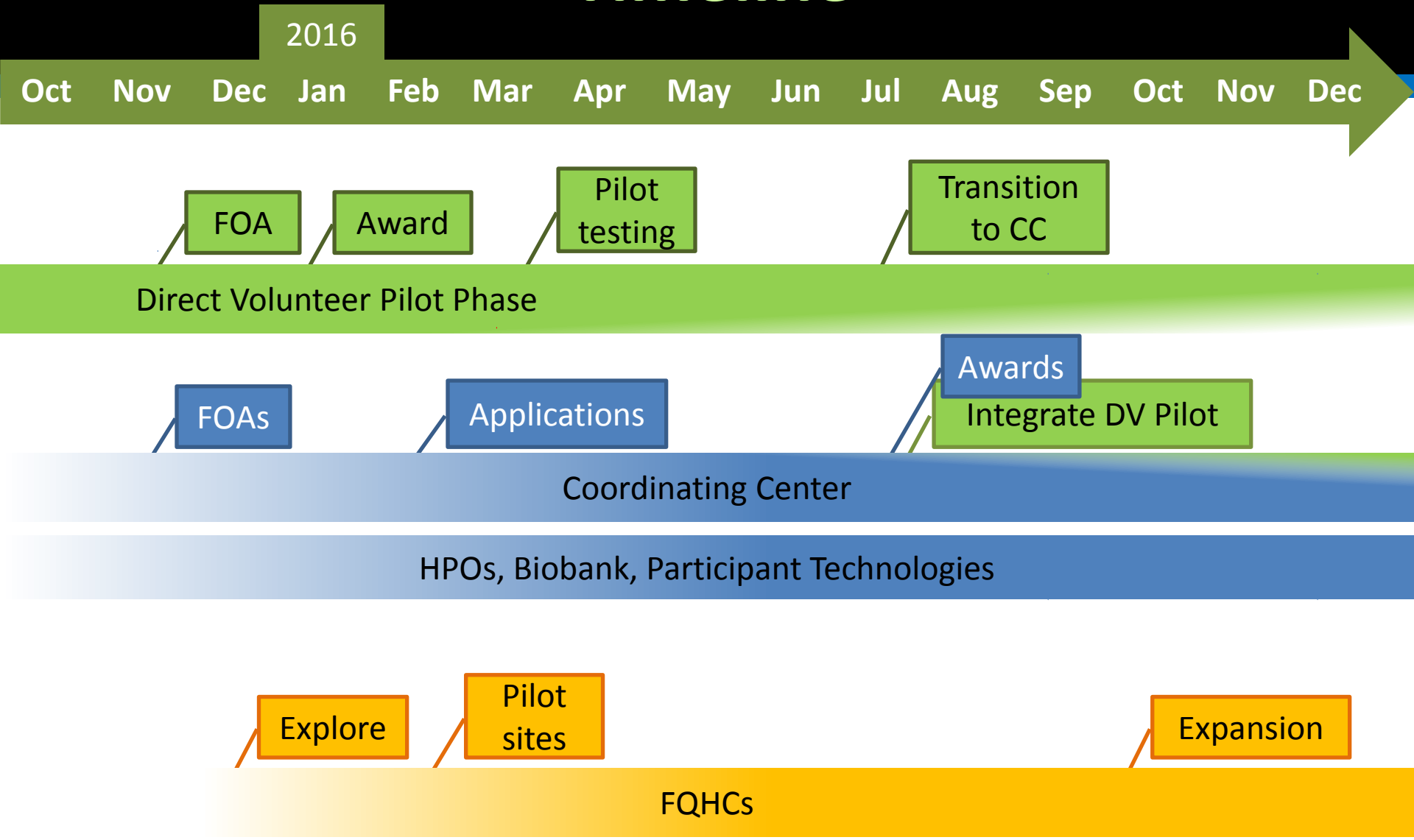
- Designed to obtain cutting edge technology, often from non-traditional sources, and to allow a high degree of flexibility

… more to come later today

PMI Cohort Program Funding Opportunities

Title / Type	Year 1 $	Number of awards	Project Period	Application	Award
Direct Volunteers Pilot Studies (OT)	TBD	1	1 yr	December 22, 2015	February 2016
Communication Support for the Precision Medicine Initiative Research Programs (OT)	TBD	1	2 yrs	December 22, 2015	February 2016
PMI Cohort Program Biobank (U24)	$15 M	1	5 yrs	February 4, 2016	June 2016
PMI Cohort Program Coordinating Center (U2C)	$21 M	1	5 yrs	February 17, 2016	July 2016
PMI Cohort Program Healthcare Provider Organization Enrollment Centers (UG3/UH3)	$28 M	≤7	5 yrs	February 17, 2016	July 2016
PMI Cohort Program Participant Technologies Center (U24)	$8 M	1	5 yrs	February 17, 2016	July 2016

Timeline


2016
Oct
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
FOA
Award
Pilot testing
Transition to CC
Direct Volunteer Pilot Phase
FOAs
Applications
Awards
Integrate DV Pilot
Coordinating Center
HPOs, Biobank, Participant Technologies
Explore
Pilot sites
Expansion
FQHCs

Achieving the bigger vision: More to come…

- PMI Cohort Program IRB
- PMI Cohort Program Office creation
- Synch-4-Science Pilots
- Convert FQHC Pilots into full implementation
- Health exam and biospecimen capabilities for direct volunteers
- Engage physicians, nurses, and other community medical providers
- Research use of the Cohort

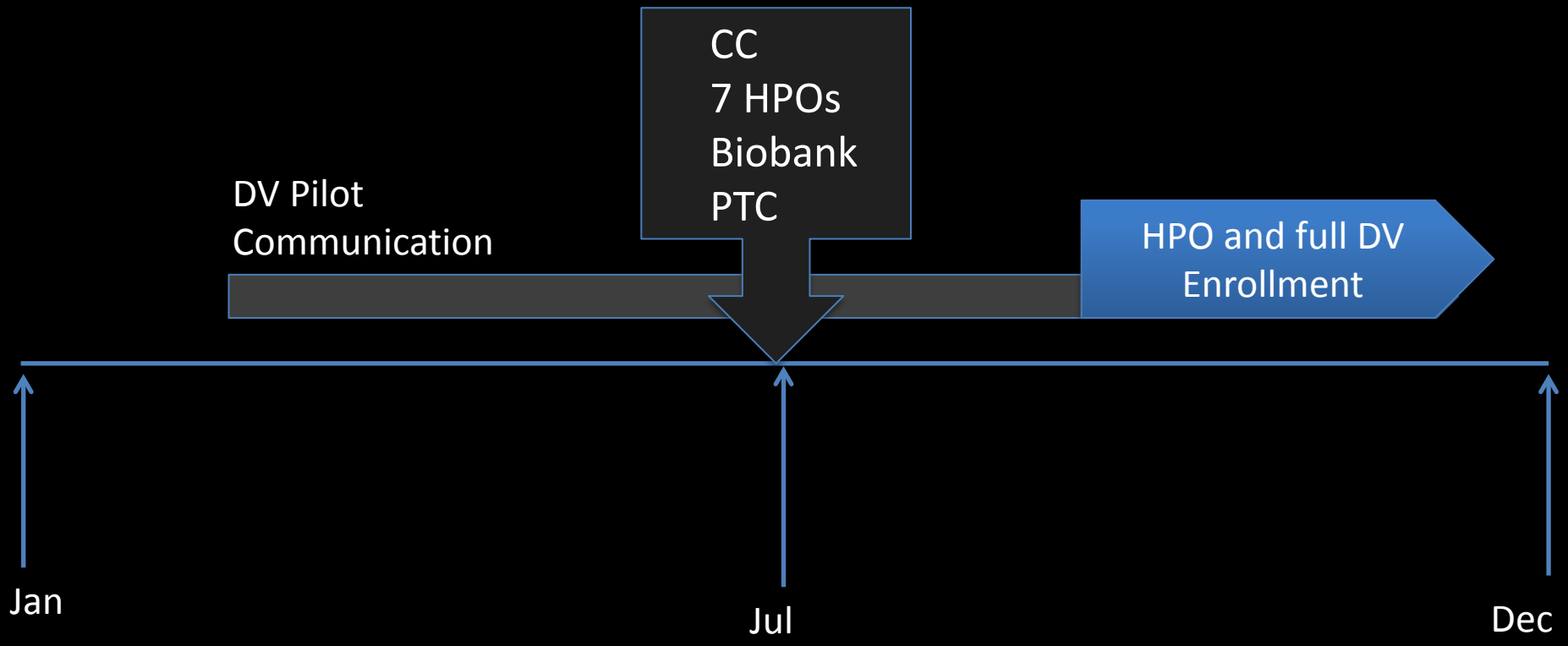
What will the PMI Cohort Program have accomplished by Dec. 2016?

- Direct volunteer recruitment and engagement strategies pilot completed
- Pilot results used to design and launch scale up of the direct volunteer program
- Strong partnerships with 5-7 major Healthcare Provider Organizations
- Successful implementation of test recruitment sites in 5 FQHCs
- ~79,000 engaged participants fully consented and enrolled in the Cohort
- Collection of biospecimens from at least 25,000
- Sync4Science FHIR method pilot complete
- Functioning data platform to allow collection of different types of data
  - Secure environment accessible to researchers
  - Participants see info about themselves according to their preferences
- 8-10 research studies using cohort data underway

Thank you!

Work to do:
Preliminary Thoughts

Development of the Baseline Core Protocol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7 HPOs
Biobank
PTC
DV Pilot
Communication
HPO and full DV
Enrollment
Jan
Jul
Dec

What will we collect? What will we measure?

- Participant provided info
- Phenotyping: Physical measurements, lab analyses
- Genetic measures
- Stored biospecimens – blood and urine
- Data extracted from EHR
- Data from mobile devices

One core principle

The Baseline Protocol will be developed cooperatively by the Steering Committee and the PMI Cohort Program Director with advice and input from you, the Advisory Panel, and from NIH PMI Cohort Program Staff.

This is the beginning of a consultative process …

Other key principles

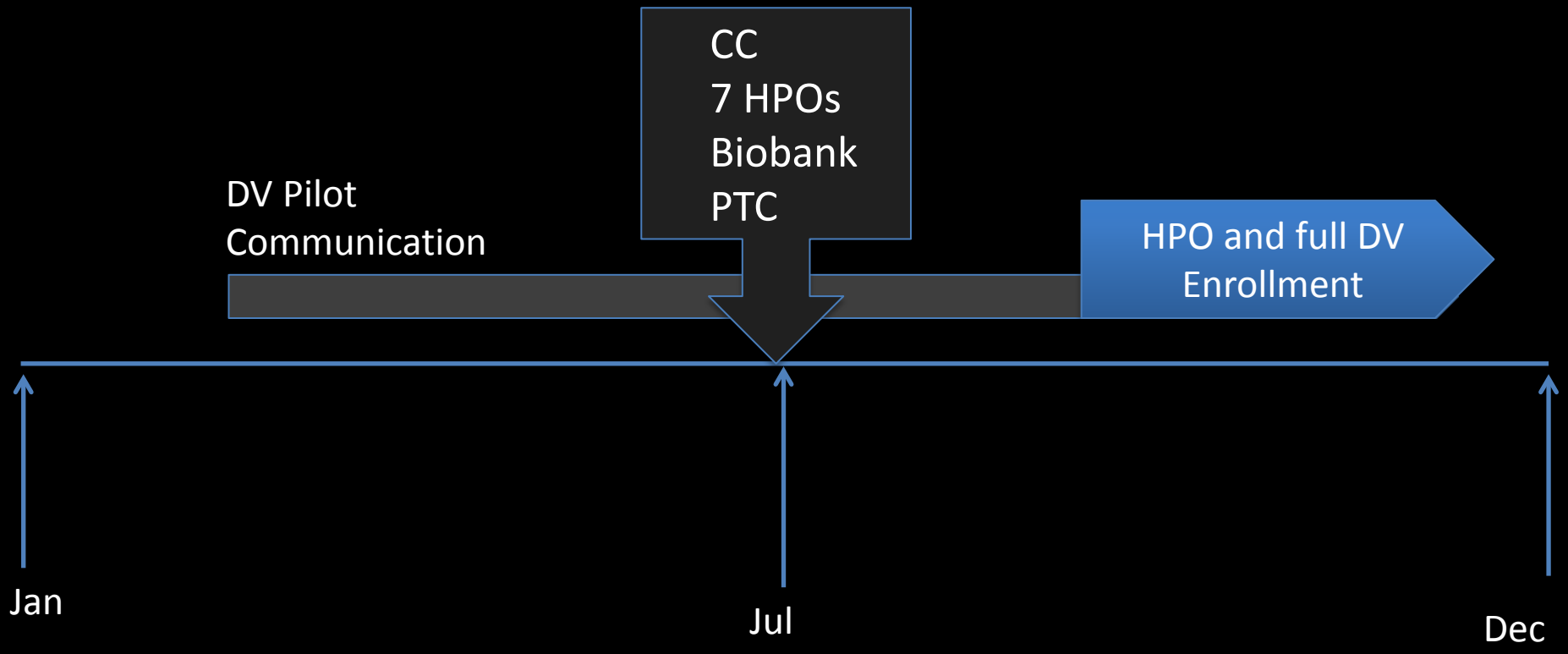
- We need to invest PMI Cohort Program resources in elements of maximum value both to participants and researchers
- We need to interact regularly with participants – and learn what interests participants, and maintains engagement

A few other concerns

- Baseline enrollment protocol must be simple
  - Is the measure of interest to participants and will it help increase engagement?
  - Is the measure important for subgroup development?
- Other criteria
  - Cross walk with other large cohorts
  - For PE - Simple to implement with reasonable consistency with personnel of variable training
  - For IT - EHR elements should be drawn from variables consistently defined – eg. Rx Norm

Early phase - Health IT data

- Expect to have both core set of central data and set of HPO federated data - including much legacy data
- Basic data base structure to be proposed by applicants, but likely to be built on architecture developed by I2B2 and PCORnet
- Certain elements – medication lists, medical condition list are now reasonably standardized
- For DVs, will depend upon ‘Blue Button’ and emerging FHIR standards – Sync4Science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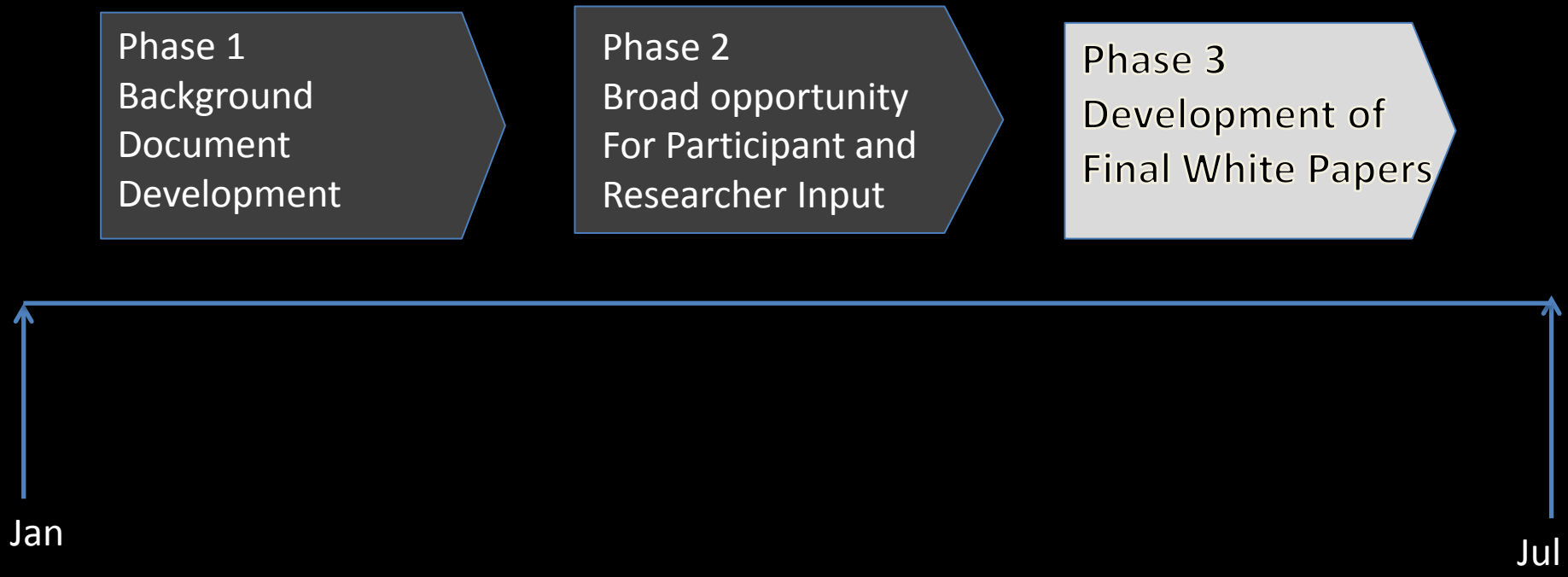
Phase 1
Background
Document
Development
Phase 2
Broad opportunity
For Participant and
Researcher Input
Phase 3
Development of
Final White Papers
Jan
Jul

Proposed White Paper Topics:

1. *Participant Provided Information*:
   - What is the core information to be provided by all participants considered enrolled in the cohort?
   - What are additional major domains of participant provided information, and what are critical elements to capture in each domain in the initial enrollment phase?
   - Is there additional core information that should be gleaned from smart phone enrollees in the enrollment phase?

Proposed White Paper Topics (cont.):

2. Phenotyping - Physical Evaluation

- What should be the components of the initial physical evaluation – what should be included?
- Should the baseline protocol differ for HPO and DV volunteers, given the different facilities and expertise available?

Proposed White Paper Topics (cont.):

3. Biospecimens

- What specimens should be collected and how should they be processed?
- What accommodations in the collection protocol are appropriate for DV enrollees, given the different facilities available?

4. *Electronic Health Records*

- What are the core data elements to be extracted initially from the EHR for all HPO participants, and what are the technical requirements to achieve this?
- What are the elements that can be extracted from S4S data

Proposed White Paper Topics (cont.):

5. Genetic measures and lab tests

- What should be measured initially?

6. Enrollment of family members

- What are the key issues that need to be considered in extending enrollment to family members?


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Phase 1: NIH staff, in consultation with you and potential participants, will draft Background Papers

January- February

Main components

- Statement of the problem
- Approach used in other major cohort studies (including international cohorts)
- A summary, when possible, of what is known about participant acceptability, including whether data has been returned to participants and impact on engagement, both overall and in relevant subpopulations
- A summary of lessons learned in previous studies
- Resource implications; participant burden
- A non-technical language summary would also be prepared

Phase 2: Broad opportunity for input

March- April

- An on-line forum for comment and input will be set-up
- Background papers will serve as the starting point
- Input will be invited from a variety of stakeholders: From potential participants, from the DV initial volunteers
- Will expect on-going input from you, from the research community

Phase 3: Final White Paper Development

May

- With continued consultation with you, the Advisory Panel and benefiting from the external comments received in Phase 2, final White Papers would be drafted
- These documents would serve as guidance for the PMI Cohort Program Director and Steering Committee in the initial phases of the RFA awards

Advice, please:

- Process

- Topic list
  - Participant provided information
  - Phenotyping
  - Specimens
  - Genetic measures
  - EHR
  - Family enrollment