

Ongoing Research and Planning for New Research Program on Post Acute Sequelae of SARS-CoV-2 Infection (PASC)

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February 26, 2021

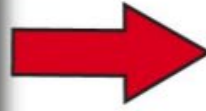


NIH Research on COVID-19

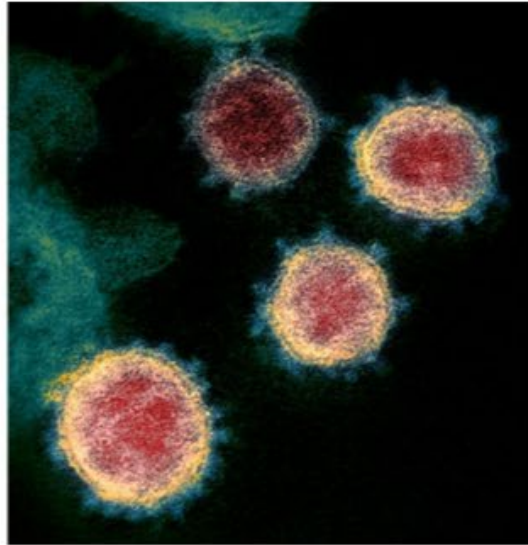
Therapeutics



Diagnostics



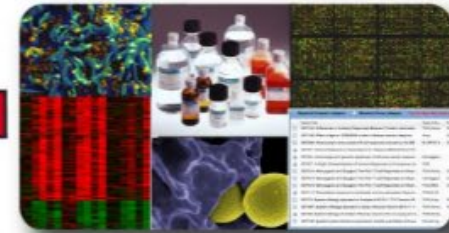
Natural History



Vaccines



Research Resources



Basic Research

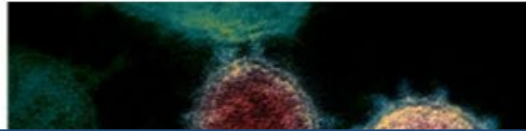


NIH Research on COVID-19

Therapeutics



Vaccines

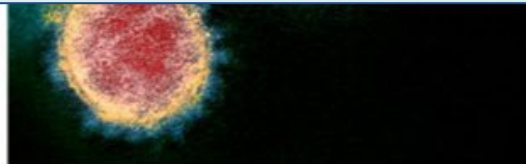


How to address an emerging problem:
recovery from SARS-CoV-2 infection?

Natural History



Basic Research



The Post-Acute Sequelae of SARS-CoV-2 Infection: Symptom clusters overlap with ME/CFS

Fatigue in almost 99% of those with post-acute sequelae. Prevalence of post-exertional malaise maybe as high as 90%.

Neurologic

- Memory/word finding difficulties
- Concentration difficulties, e.g., “brain fog”
- Executive function difficulties
- Sleep disorders
- Pain syndromes - muscle, joint
- Abnormal sensations - tingling
- Headache
- Postural Orthostatic Tachycardia
- Abnormal smell/taste
- Visual abnormalities
- Dizziness/balance problems
- Confusional state/psychosis

Cardio/Pulmonary

- Shortness of breath
- Dry cough
- Chest pain
- Exercise intolerance
- Postural Orthostatic Tachycardia
- Palpitations/ Fast heart rate
- Myocarditis
- Pulmonary fibrosis

Mental Health

- Post traumatic stress disorder
- Anxiety
- Depression

Gastrointestinal

- Diarrhea
- Decreased appetite
- Nausea
- Abdominal pain

Other

- Elevated temperature
- Chills, flushing sweats
- Sore throat
- Extreme thirst
- Skin changes
- Menstrual changes

See Davis HE et. al. (2021) Characterizing Long Covid in an International Cohort: 7 months of symptoms and their impact. medRxiv preprint
<https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2>

There are many ongoing NIH resources that can be leveraged to better understand COVID recovery

Electronic Health Records and Health Systems studies; 10 million+ collective participants. E.g.,

- National COVID Cohort Collaborative (N3C) (EHR-based COVID)
- eMERGE: combines DNA biorepositories with electronic medical record (EMR) systems
- North American – AIDS Cohort Collaboration on Research and Design
 - Corona infectious virus epidemiology team (CIVETs)
- All of Us: COVID survey, antibody testing, and more

40+ studies with cohorts of COVID-19 cases; 20,000+ collective participants. E.g.,

- NCCAPS: longitudinal study of patients with cancer/diagnosed with COVID
- COVNET: GWAS to identify genetic variants associated with susceptibility to COVID
- PETAL Network/BLUE CORAL: collect comprehensive data on hospitalized patients with COVID-19
- Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC)
- RADx-UP: diagnostics in underserved populations
- Pediatric studies: PRISM, PreVAIL kids, MUSIC, ARC, AICORE-kids

30+ studies with cohorts with pre-pandemic deep phenotyping (esp. neurologic, cardiac, or pulmonary); 100,000+ collective participants. E.g.

- Collaborative Cohort-of-Cohorts for COVID-19 Research (C4R)
 - Includes 14 cohorts: ARIC, CARDIA, Framingham, HCHS, Jackson, MASALA, MESA, Strong Heart, COPDGene, FIP, SARP, SPIROMICS, REGARDS, NOMAS
- HIV studies: REPRIEVE, CNICS,
- PARIS (pediatric AHRF), SPARTA (emphysema), ABCD (diabetes),
- ECHO (ped./environment)

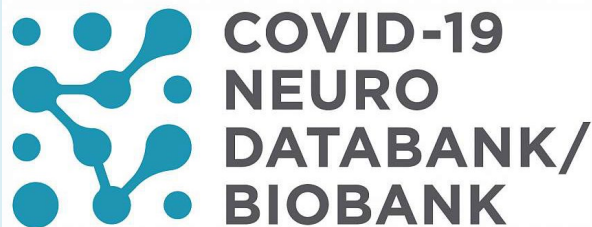
NINDS supported projects related to COVID + ME/CFS

COVID Research Supplement Program

Notice of Special Interest (NOSI): Availability of Urgent Competitive Revisions and Administrative Supplements For Research on Biological Effects of the 2019 Novel Coronavirus on the Nervous System
Notice Number: NOT-NS-20-051

E.g., award to Leonard Jason (PI) at DePaul University ([R01-NS111105](#))

- Add-on study to college student cohort (~4500 young adults) to assess long-term health of those that have contracted COVID-19
- This is building on an ongoing ME/CFS study re post EBV fatigue syndrome



NIH [NeuroCOVID](#) Project (at NYU Langone)

- Database will collect information from clinicians about COVID-19-related neurological symptoms, complications, and outcomes as well as COVID-19 effects on pre-existing neurological conditions
- Associated biospecimen bank

Ongoing Intramural studies: Led by Avi Nath, Brian Walitt, Bryan Smith, and others

Intramural studies addressing long term neurological symptoms associated with COVID-19

Natural History of Post-Coronavirus Disease 19 Convalescence

Avi Nath (NINDS), Brian Walitt (NINR)

To observe and describe the range of medical syndromes that occur following an acute COVID-19 infection

Study population: 1000 adults who are within six months of their convalescence from an acute COVID-19 infection

Starting with telephone interviews and internet-based questionnaires; following phases = in depth evaluation at CC; focus on identifying patients who overlap with ME/CFS; longitudinal follow up



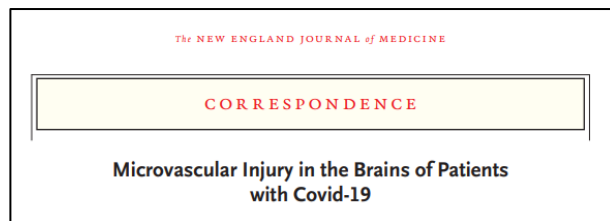
An Observational Study of Neurologic Function after COVID-19 Infection

Avi Nath (NINDS), Bryan Smith (NINDS)

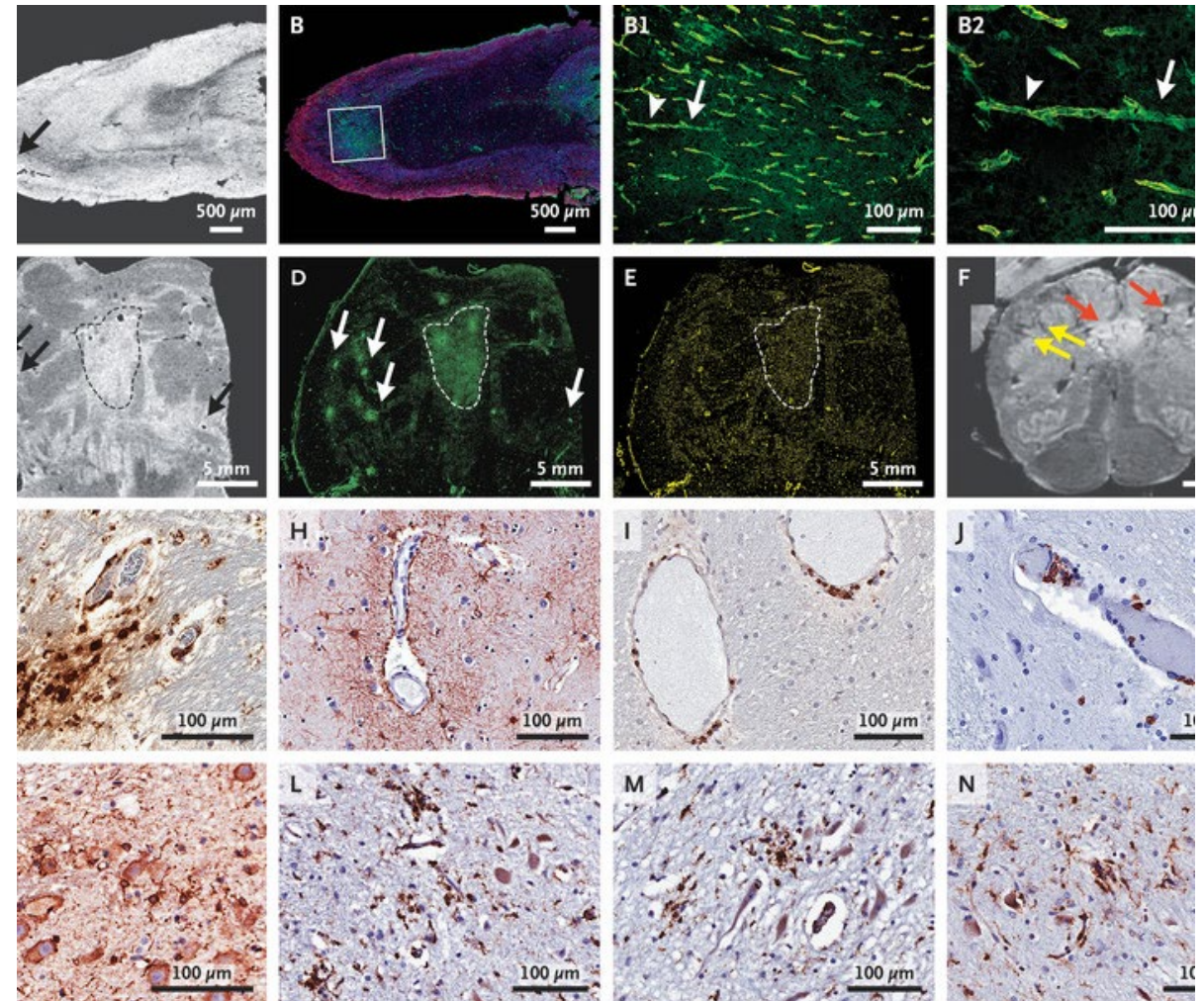
To investigate structural abnormalities by brain MRI and other components of neurologic function in those with prior SARS-CoV-2 infection and persistent neurologic symptoms

Is SARS-CoV-2 in the brain?

- Post-mortem study of brains of individuals who had COVID-19
- No evidence of viral infection in brain
- Widespread evidence of inflammation and damage, including:
 - Multifocal breakdown of the blood brain barrier, small infarcts, microhemorrhages, inflammatory infiltrates, and microglial nodules,
- Infection can lead to blood clots → stroke

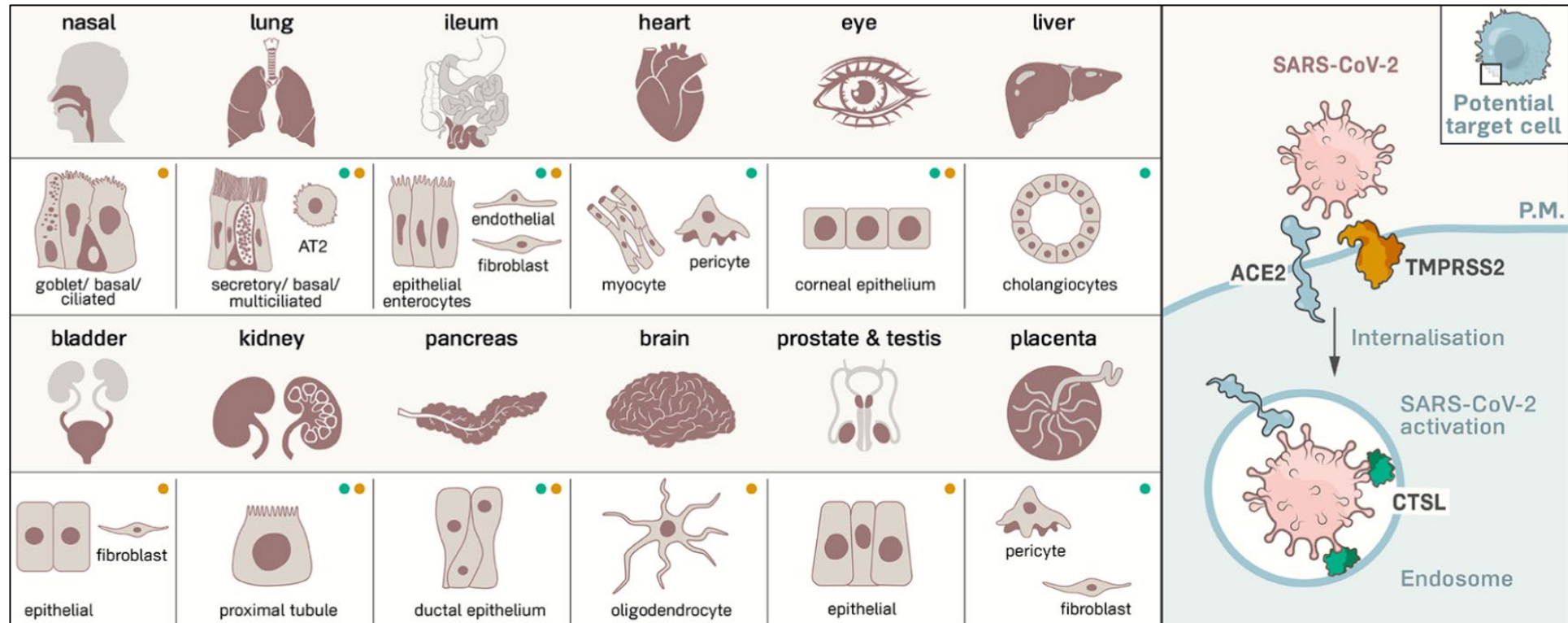


Nath et al, [NEJM](#), NINDS



Pathological Studies of Microvascular Injury in the Brains of Patients Who Died from COVID-19

COVID-19 Affects Multiple Organs



[The Scientist](#), April 2020

NIH Post Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative

NIH Post Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative

Coronavirus Response and Relief Supplemental Appropriations Act, 2021

- NIH Office of the Director received \$1.15 billion over 4 years for research and clinical trials related to long-term studies of COVID-19

NIH is leveraging Other Transaction Authority (OTA), which offers flexibility and the ability to engage partners in collaborative innovation and problem solving

Just announced!

<https://covid19.nih.gov/funding/open-funding-opportunities>

[Recovery Cohort - Research](#)

[Opportunity](#) soliciting proposals for studies involving: (a) clinical recovery cohorts, (b) EHR and other real-world data, and (c) autopsy cohorts; proposals must be received by **March 23**

[Cores - Research Opportunity](#) soliciting proposals for: (a) a Data Resource Core, (b) a Clinical Studies Core, and (c) a Biospecimen Core; proposals must be received by **March 16**

NIH PASC Research

Goal

- ▶ Rapidly improve our **understanding** of and **ability to treat** and prevent PASC

Key Scientific Questions

- 1 What are the clinical spectrum of and biology underlying recovery from acute SARS-CoV-2 infection over time?
- 2 For those patients who do not fully recover, what is the incidence/prevalence, natural history, clinical spectrum, and underlying biology of this condition? Are there distinct phenotypes of patients who have prolonged symptoms or other sequelae?
- 3 Does SARS-CoV-2 infection initiate or promote the pathogenesis of conditions or findings that evolve over time to cause organ dysfunction or increase the risk of developing other disorders?

**Acute
SARS-CoV-2
Infection Cohorts**

**Post-Acute
SARS-CoV-2
Infection Cohorts**

**NIH
SARS-CoV-2
Recovery
Cohort**

**5-10K PASC
over 3-6 months**

*What are the clinical spectrum
of and biology underlying
recovery from acute SARS-CoV-2
infection over time?*

*For those patients who do
not fully recover or develop
new sx/sequelae, what is
the clinical spectrum and
underlying biology?*

*Does SARS-CoV-2 infection initiate or
promote the pathogenesis of conditions or
findings that evolve over time to cause
organ dysfunction or increase the risk of
developing other disorders?*

EHR-/Health Systems-Based Studies

Research Approach

- 1 **Establish a SARS-CoV-2 Recovery Cohort** to yield ~ 5-10K PASC cases over the next 3-6 months
 - ▶ SARS-CoV-2 infection case-driven and multi-disciplinary prospective assessment of PASC
 - Incidence/ prevalence, epidemiology, clinical spectrum, outcomes, risk factors
 - Leverage ongoing fit-for-purpose cohorts as well as new cohort studies
 - Includes children and adults (including pregnant women) and inclusive participation
 - Proactive community engagement as integral element
 - Will inform design of treatment and prevention strategies
- 2 **Leverage EHR- and Other Real-World Data-Based analyses**
- 3 **Autopsy Studies**

Notes:

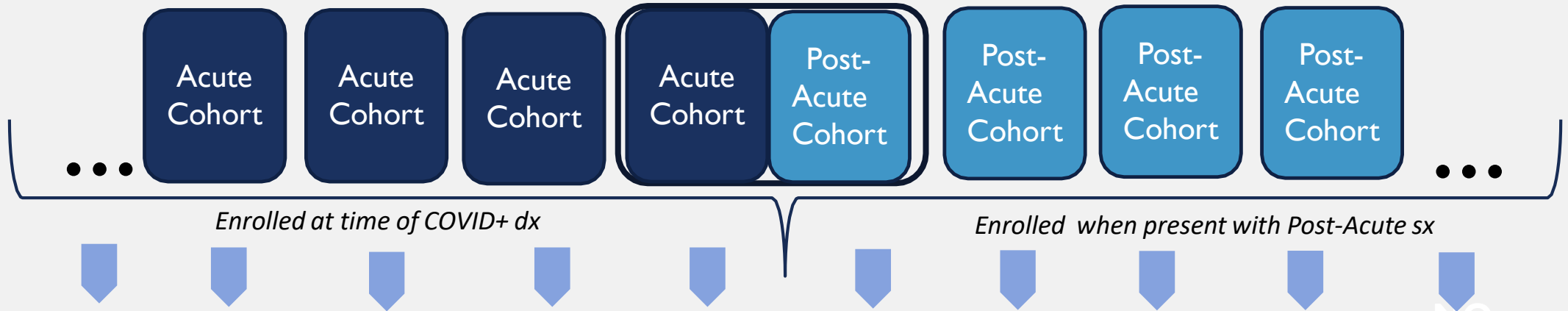
Includes
Peds Cohorts
Studies

Includes new
and leveraged
ongoing studies

Broad
Spectrum of
Recovery
Phenotypes

Individual
protocols
but
use of
core common
protocol
elements

SARS-CoV-2 Recovery Clinical Study



Enrolled at time of COVID+ dx

Enrolled when present with Post-Acute sx

Clinical Characterization/Phenotyping

**Streamlined core protocol elements (exam, labs, functional tests, imaging)
to capture spectrum of PASC**

Examples of assessments could include:

- Imaging (CT, MRI, Echo)
- Functional Assessments (PFTs, 6MW, ETT)
- Neuropsychiatric assessments (screening, questionnaires, testing)
- Psychosocial Factors, SDoH
- Immunophenotyping
- Biospecimens (Biomarkers, Multi-omics)
 - More in-depth assessments as indicated (e.g., fpgPET)

SARS-CoV-2 Recovery Cohort

PASC Initiative Components

SARS-CoV-2 Recovery Meta-Cohort

- ▶ Clinical Recovery Cohort
- ▶ Autopsy Cohort (Acute and PASC)
- ▶ EHR- and Other Real-World Data-Based Studies



Investigator Consortium

All study investigators will work together to:

- ▶ Conduct rapid systematic screening and follow-up evaluations of infected individuals, to provide a resource for in-depth multi-disciplinary phenotyping, and to pool data and share biospecimens and data from across studies
- ▶ Develop a streamlined set of common core protocol elements (specific hypotheses, design elements, screening evaluations, exams, lab tests, functional assessments, imaging, etc.) and to provide a collaborative for multi-disciplinary phenotyping

PASC Initiative Components

- ▶ The goals of the Recovery Cohort and Investigator Consortium will be supported by **administrative coordination** and **oversight** as well as **three cores**:
- ▶ Clinical Science Core
- ▶ Data Resource Core
- ▶ PASC Biorepository Core



PASC Initiative Components

- ▶ The goals of the Recovery Cohort and Investigator Consortium will be supported by **administrative coordination** and **oversight** as well as **three cores**:
- ▶ **Clinical Science Core**

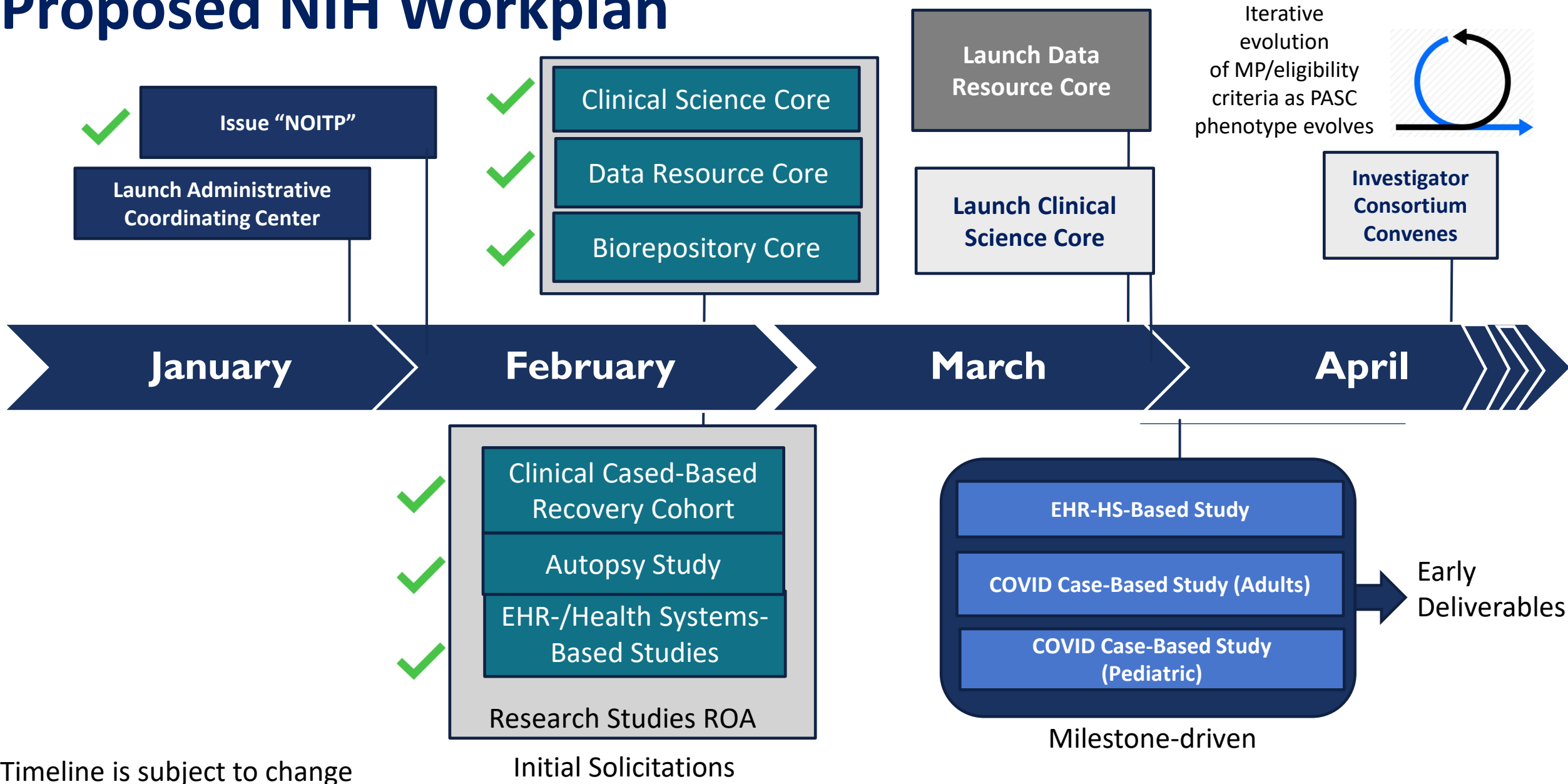
Community and patient engagement

“The Clinical Science Core will provide....

Leadership of a Patient Engagement Working Group (e.g. a Community Advisory Board) to engage PASC patients, physicians and other stakeholders in **shaping the research agenda initially and iteratively** as research questions evolve, to **work with investigators in disseminating information on the rationale and ethical basis for conducting the PASC studies**, and to **provide feedback from the community** at large on the research. The Patient Engagement Working Group should be diverse and represent a broad range of patients and communities...”



Proposed NIH Workplan



Learn More: Technical Assistance Workshop

March 1, 5 PM ET

- **Audience:** Potential applicants for Research Opportunities
- **Purpose:** To enhance potential applicant understanding of the Research Opportunity Announcements and facilitate preparation of responsive applications
- **Topics:**
 - Overview of the vision and specific objectives of PASC initiative highlighting key scientific/research elements of the ROAs including the three cores and the three specific research components
 - Overview of the OT mechanism and application process and requirements
 - Answer prospective applicant questions



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Webinar Registration



NIH Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Technical Assistance Webinar

Please register for the NIH PASC Technical Assistance Webinar via the required fields below. If you would like to pre-submit any questions to the team, please use the optional field at the end of the form.

Registration available at:
<https://covid19.nih.gov/funding/open-funding-opportunities>

Discussion