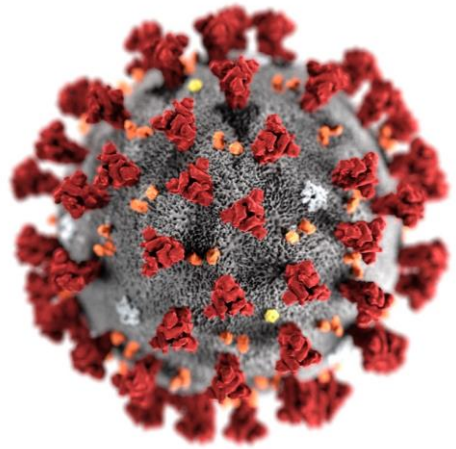
CONNECTS



Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies

Launching CONNECTS: A Partnership Between Research Triangle Institute, Vanderbilt University Medical Center, and NHLBI

Sonia Thomas, DrPH RTI and Gordon Bernard, MD VUMC

September 11, 2020

NIH National Heart, Lung, and Blood Institute

Collaboration of 34+ Networks and 1,000+ Sites

INSIGHT Clinical Research Network

NIH SIREN Emergency Trials Network

RAPID COVID COAG

CTSN CARDIOTHORACIC SURGICAL TRIALS network

ISCHEMIA

LITES Linking Investigations in Trauma and Emergency Services

PETAL NETWORK Prevention & Early Treatment of Acute Lung Injury

REMAP-CAP

INVESTED NIH National Heart, Lung, and Blood Institute

IVY

VENUS

PCCRG

PrecISE PRECISION INTERVENTIONS FOR SEVERE ASTHMA

TACTIC

I-SPY The I-SPY Trials

OneFlorida Clinical Research Consortium

pcornet® The National Patient-Centered Clinical Research Network

STAR Stakeholders, Technology, and Research CRN

HEART FAILURE NETWORK

REACHnet Research Action for Health Network

PulmonaryTrials Cooperative

NATIONAL DRUG ABUSE TREATMENT CLINICAL TRIALS NETWORK

Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

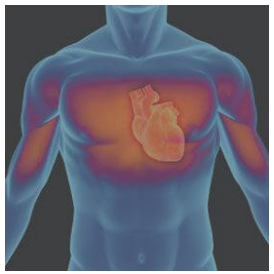
MHICC

MONTREAL HEART INSTITUTE

Université de Montréal

Pediatric Heart Network

American Lung Association.
Airways Clinical Research Centers Network



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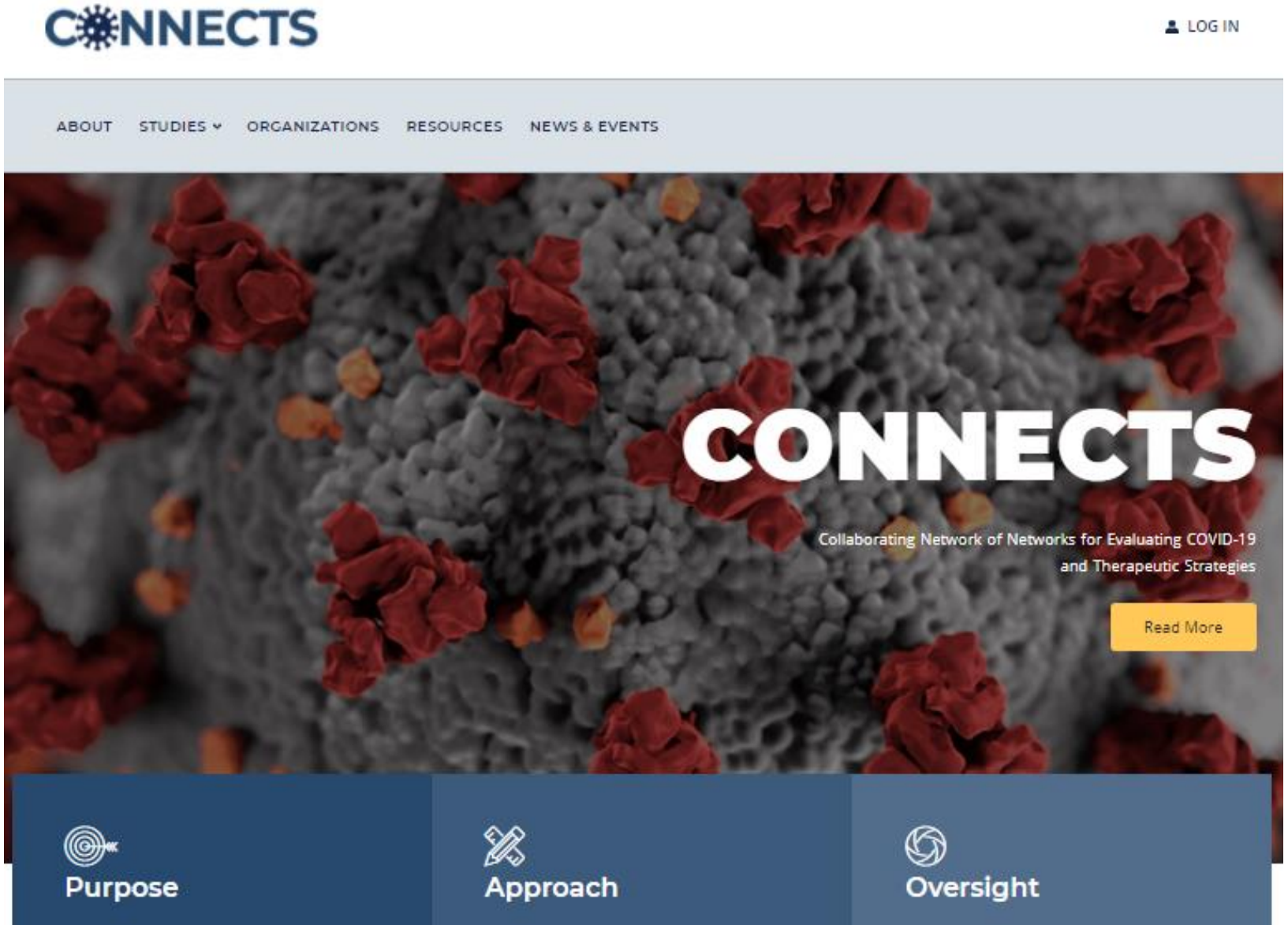
CLOT Consortium Linking Oncology with Thrombosis

TIMI Study Group
An Academic Research Organization of Brigham & Women's Hospital and an Affiliate of Harvard Medical School

CIRT Cardiovascular Inflammation Reduction Trial

Website nhlbi-connects.org



Why a CONNECTS collaborative?

Current unprecedented and urgent public health crisis

- Assemble expertise and resources in a nimble fashion
- Ensure appropriate geographic reach and expertise
- Enable resource deployment when and where needed

This collaborative transcends what any individual network may do alone

"The whole is greater than the sum of its parts"

CONNECTS Vision

- **Overarching Purpose:**
  - Test host-directed therapies for COVID-19 via rapid, efficient, collaborative adaptive platform trials aimed at helping to prevent infection, slow or halt disease progression, and speed recovery

- **Strategic approach**:
  - Fully integrate major NHLBI networks under one organizational umbrella to ensure efficiencies; standardization; collaboration; and sharing of control groups (as appropriate), resources, and data
  - Nimbly shift studies as needed, based on new knowledge and changing pandemic clinical landscape

- **Expectation:**
  - Innovative model of seamless collaboration; all set aside their own “team jerseys” to join an All-Star Team

CONNECTS Is Part of a Larger Ecosystem

Strategic direction, oversight, and key partnerships:

- NHLBI-directed
- In collaboration with BARDA; Operation Warp Speed; and as appropriate, other ICs (e.g., NIAID, NINDS)
- Engage clinical trials/networks, other NIH ICs, Clinical Data Interchange Standards Consortium
- Trials are aligned with, or formally part of, NIH ACTIV (e.g., ACTIV-4)

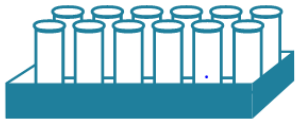
NHLBI COVID-19 Clinical Studies Framework

COVID-19+ Progression →

Prevention | Outpatient Asymptomatic | Outpatient Symptomatic | Emergency Department | Hospital Vent/CPAP-free | Hospital ICU | Conva-lescence | Recovered

Point of Care Diagnostics

Database



Biorepository and Analytics

Host-Directed Therapeutics Clinical Trials

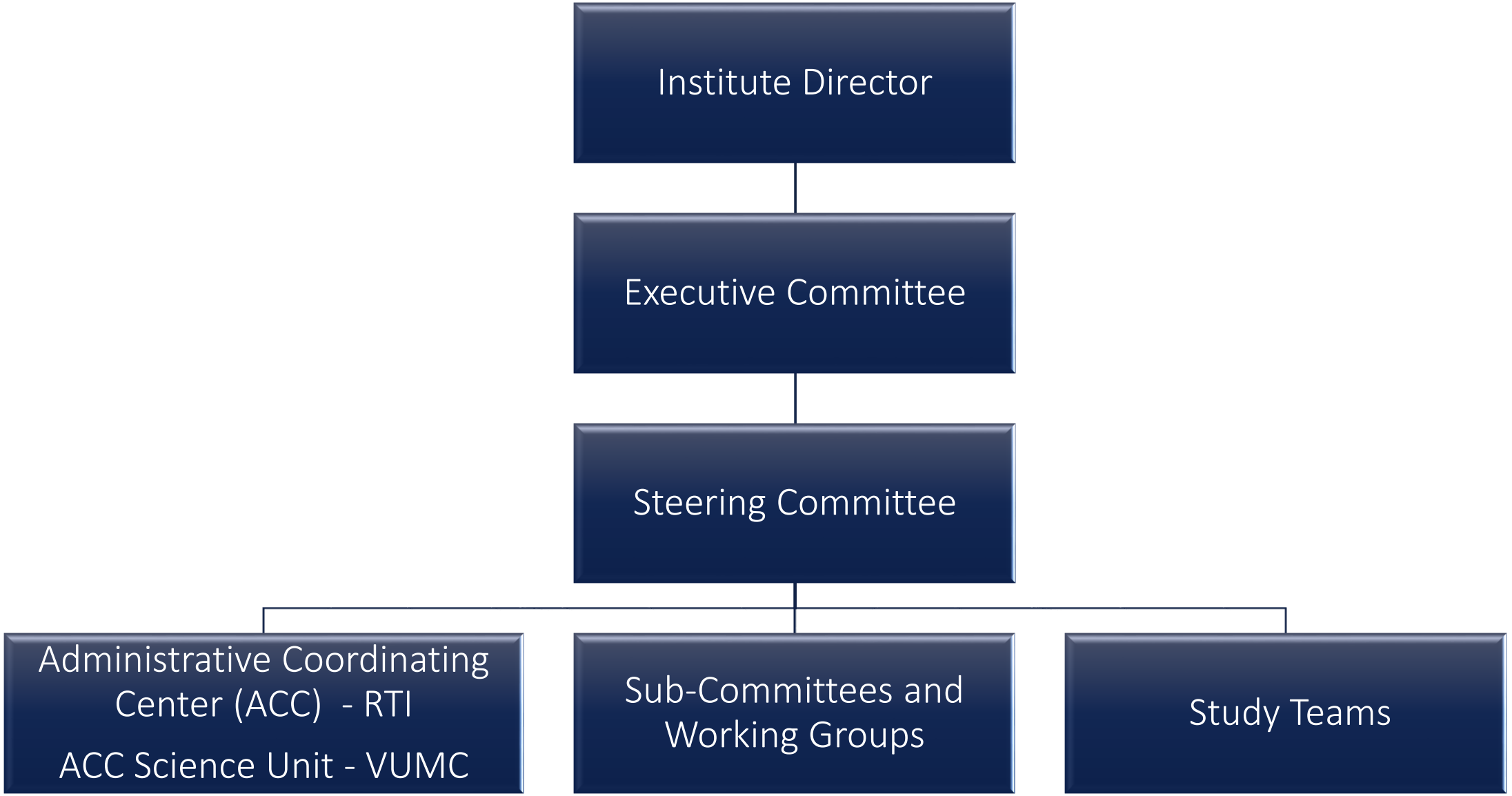
Patient Registry and Long-term Follow up

Cohort of Cohorts

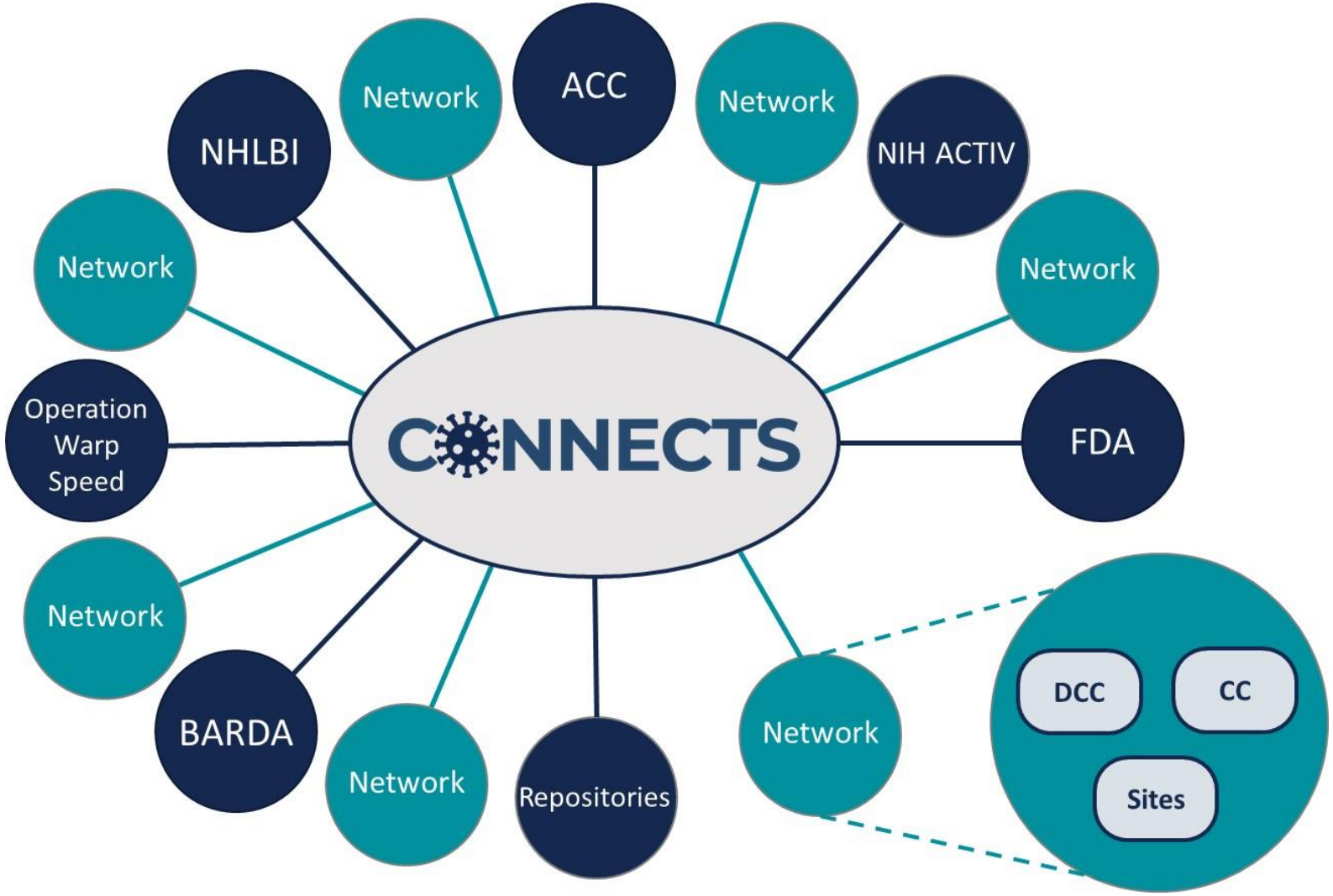
REDS-IV-P Sero-surveillance

Community-Based Research Consortium

CONNECTS Infrastructure



CONNECTS Is a Research Collaborative



A community promoting collaboration, harmonization, and sharing of scientific expertise and resources.

Steering & Executive Committee Chairs

Steering Committee

Clyde Yancy, Chair
(Northwestern University)

Serpil Erzurum, Vice-Chair
(Cleveland Clinic)

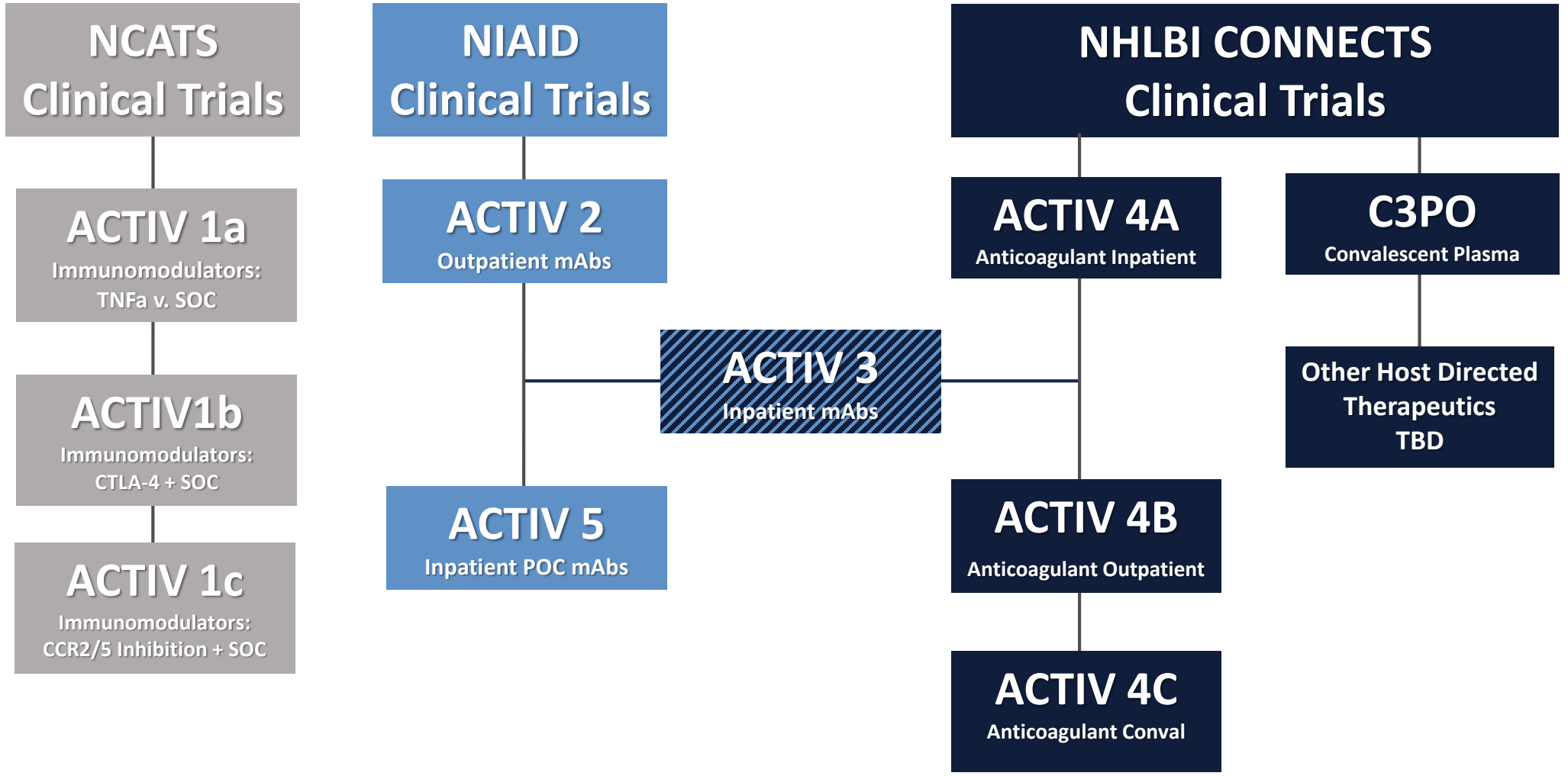
Diane Nugent, Vice-Chair
(CHOC Children's Hospital)

Executive Committee

Robert Harrington, Co-Chair
(Stanford University)

Amy Patterson, Co-Chair
(NHLBI)

CONNECTS and ACTIV Clinical Trials



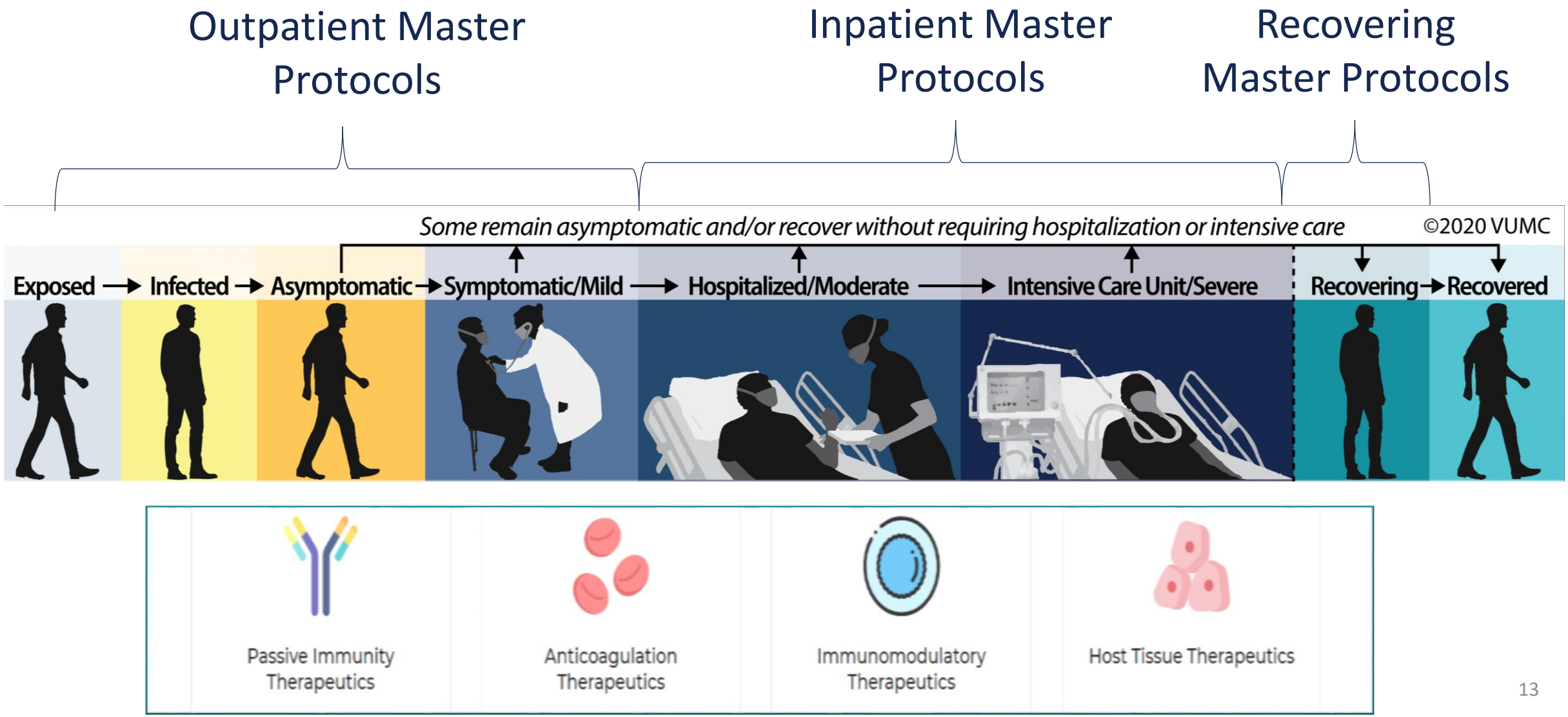
Designing New Studies

Gordon Bernard, MD

CONNECTS ACC Science Unit PI

Vanderbilt University Medical Center

Our Immediate Goal: Design and Implement Master Protocol Driven Adaptive Clinical Trials

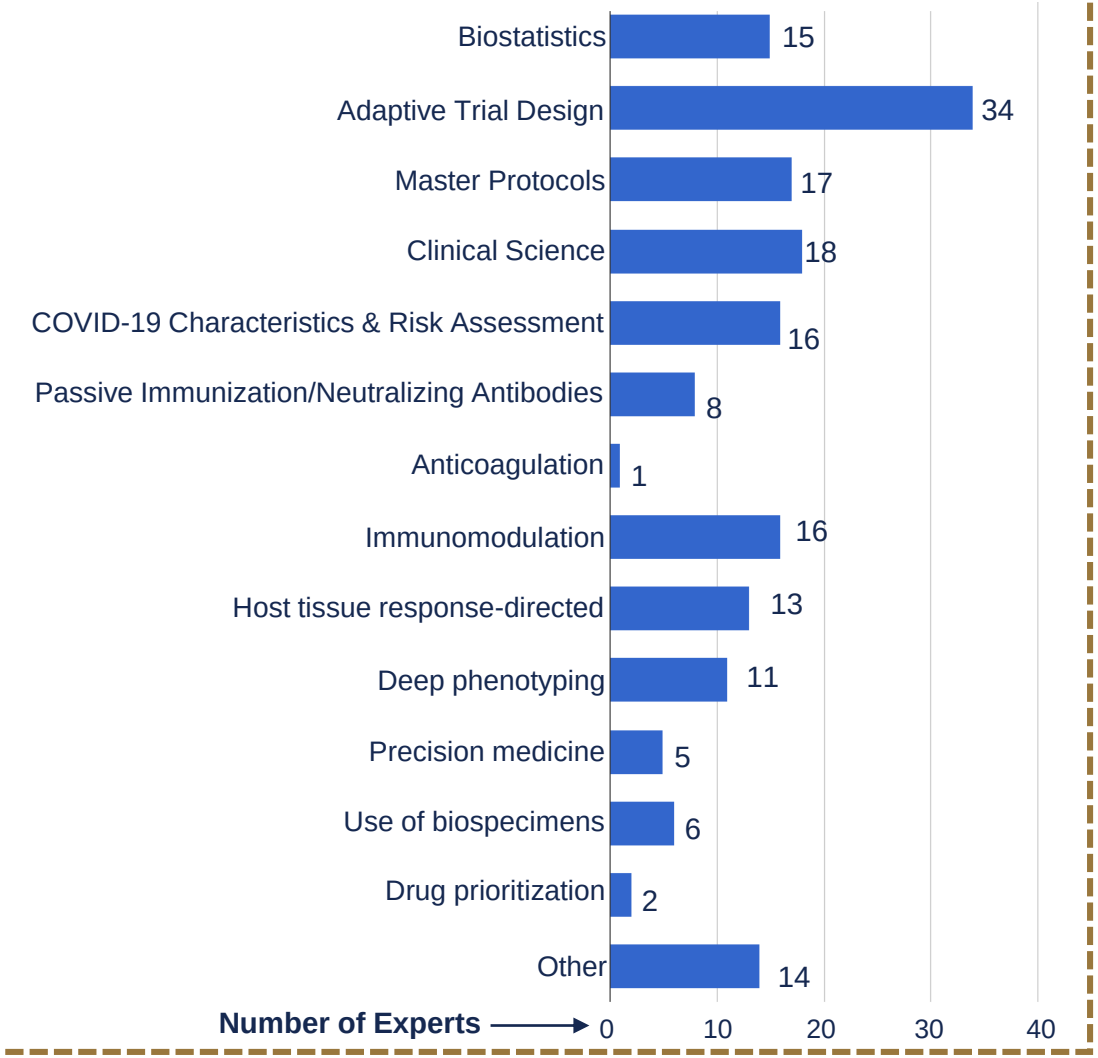


Leveraging Network Expertise for Master Protocol and Agent Prioritization leadership groups

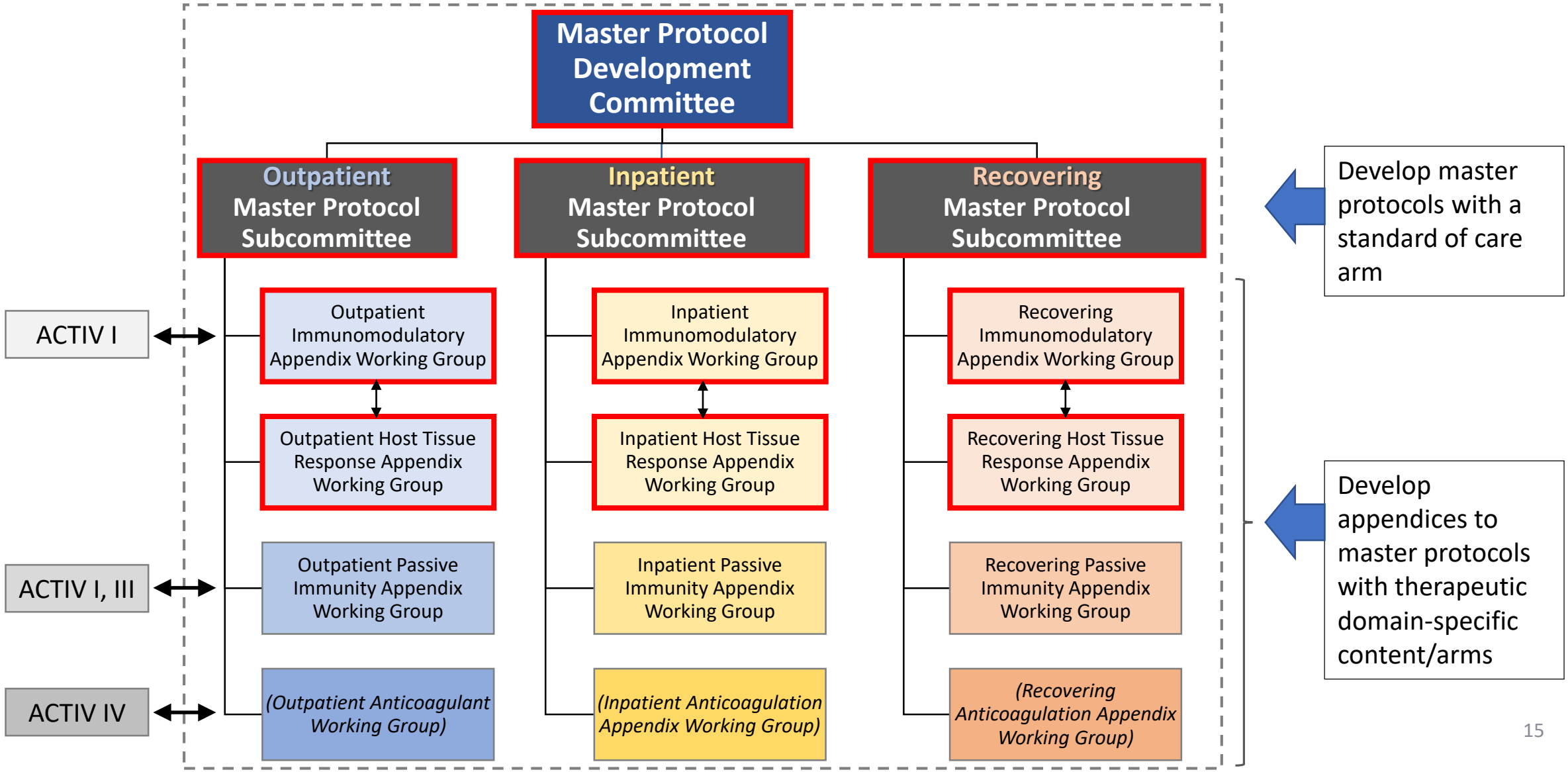
Progress to Date

- All network-nominated experts are currently engaged by the ACC.
- **Experts are serving as members in Master Protocols and Agent Prioritization committees.**
- **Additional nominations are always welcome**

Nominated Expert Areas of Expertise



Master Protocol Committee Structure:
Drafting and harmonization of master protocols across patient stages



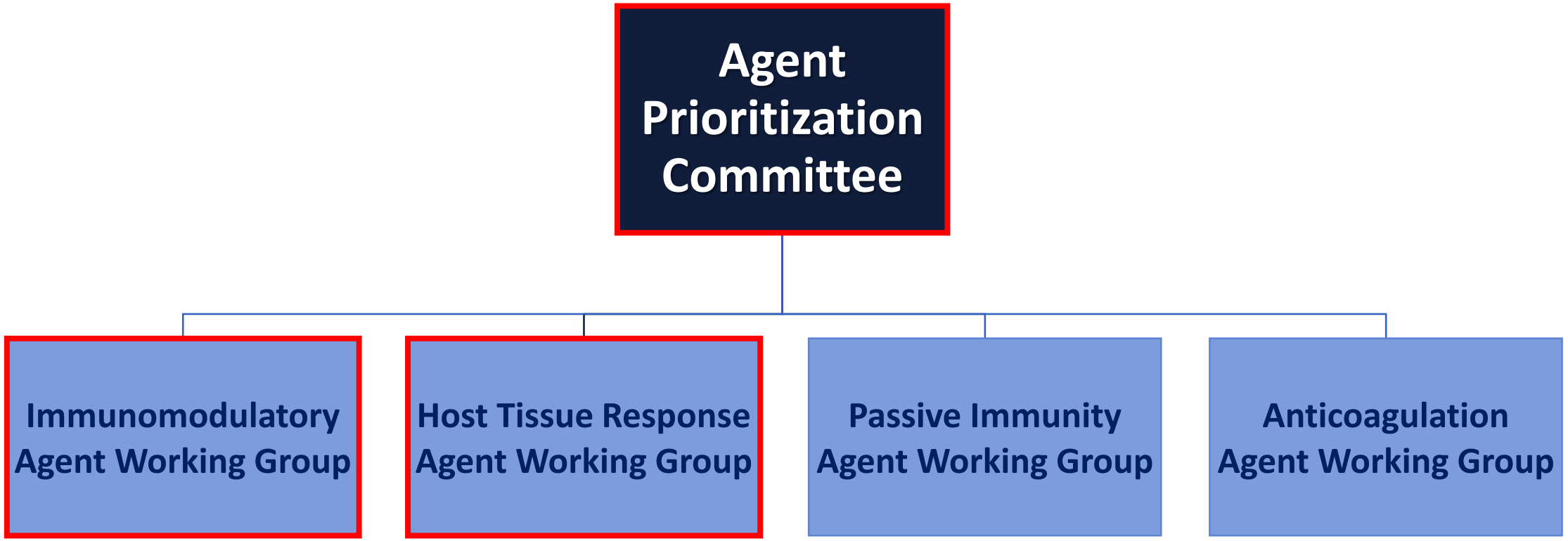
Statistical Design Concepts for COVID-19

- What are the most informative/statistically powerful outcomes?
  - Proposal: An ordered scale that includes clinically relevant and patient-centered features, that combines both safety and efficacy information, and that encompasses information pertinent across all settings and disease severities.

- What types and levels of evidence are needed to stop a trial?
  - Proposal:
  - Sequential design with frequent looks based on calendar time and a range of expected accrual rates rather than enrollment so that decisions can be made in a timely way.
  - Bayesian interim analysis methods incorporating a skeptical prior for efficacy, an uninformative prior for inefficacy/harm, and setting the acceptable level of evidence posterior probability such as ≥ 0.95.

NIH National Heart, Lung, and Blood Institute

Agent Prioritization Committee Structure:
Review and prioritization of potential nominated therapeutics



Overarching Agent Prioritization Committee (under construction)

Workstreams Groups

Immunomodulatory

Passive Immunity

Host-tissue Response

Anticoagulation

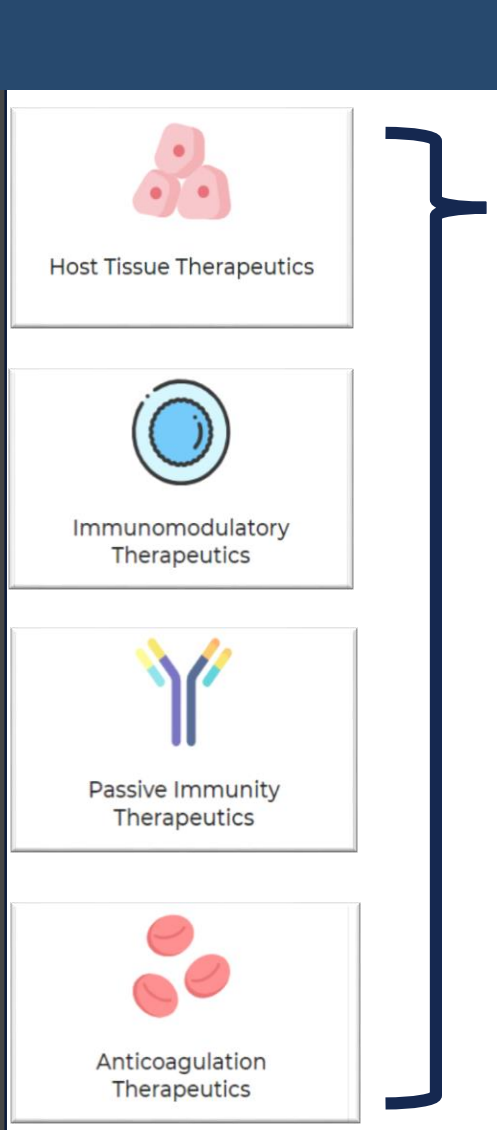
Michael Matthay[1]
Marie-Carmelle Elie[2]
Clark Files[3]
Macky Neal[4]
Richard Becker
Jeffrey Berger
Javed Butler
Ivor Douglas
Serpil Erzurum
Michael Felker
Judith Hochman
Thomas R. Martin
Chad Miller
Duane Mitchell
Thomas Ortel
Liise-Anne Pirofski
Todd Rice
Paul Ridker
Wes Self
Chris Seymour

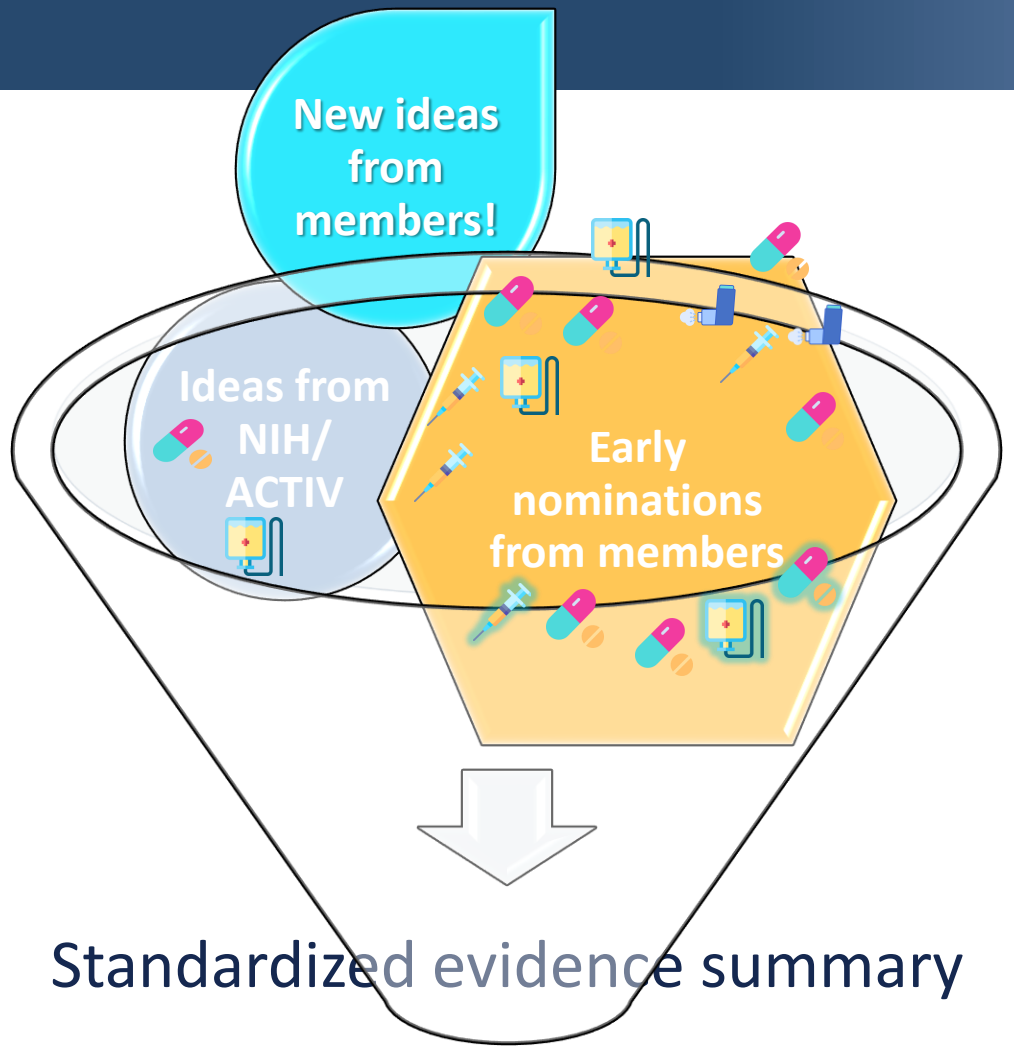
Additional Members

Neil Aggarwal – NIH/NHLBI
Gordon Bernard – CONNECTS ACC VUMC Science Unit PI
Ann Farrell – FDA, DNH, CDER/FDA
Mary J. Homer – Chief, RNC, BARDA
Zorina Galis – NIH/NHLBI
David Goff – ***Committee Co-Chair,*** NHLBI Dir, DCVS
James Kiley – ***Committee Co-Chair***, NHLBI Dir, DLD
Andrei Kindzelski - NIH/NHLBI
Tony Punturieri – NIH/NHLBI
Lora Reineck – NIH/NHLBI
Yves Rosenberg – NIH/NHLBI
Sonia Thomas – CONNECTS ACC PI

Workstreams Chairs: [1] Immunomodulatory; [2]*Proposed* Passive Immunity; [3]Host-tissue Response; [4]*Proposed* Anticoagulation.

Nominations can and should come from multiple places

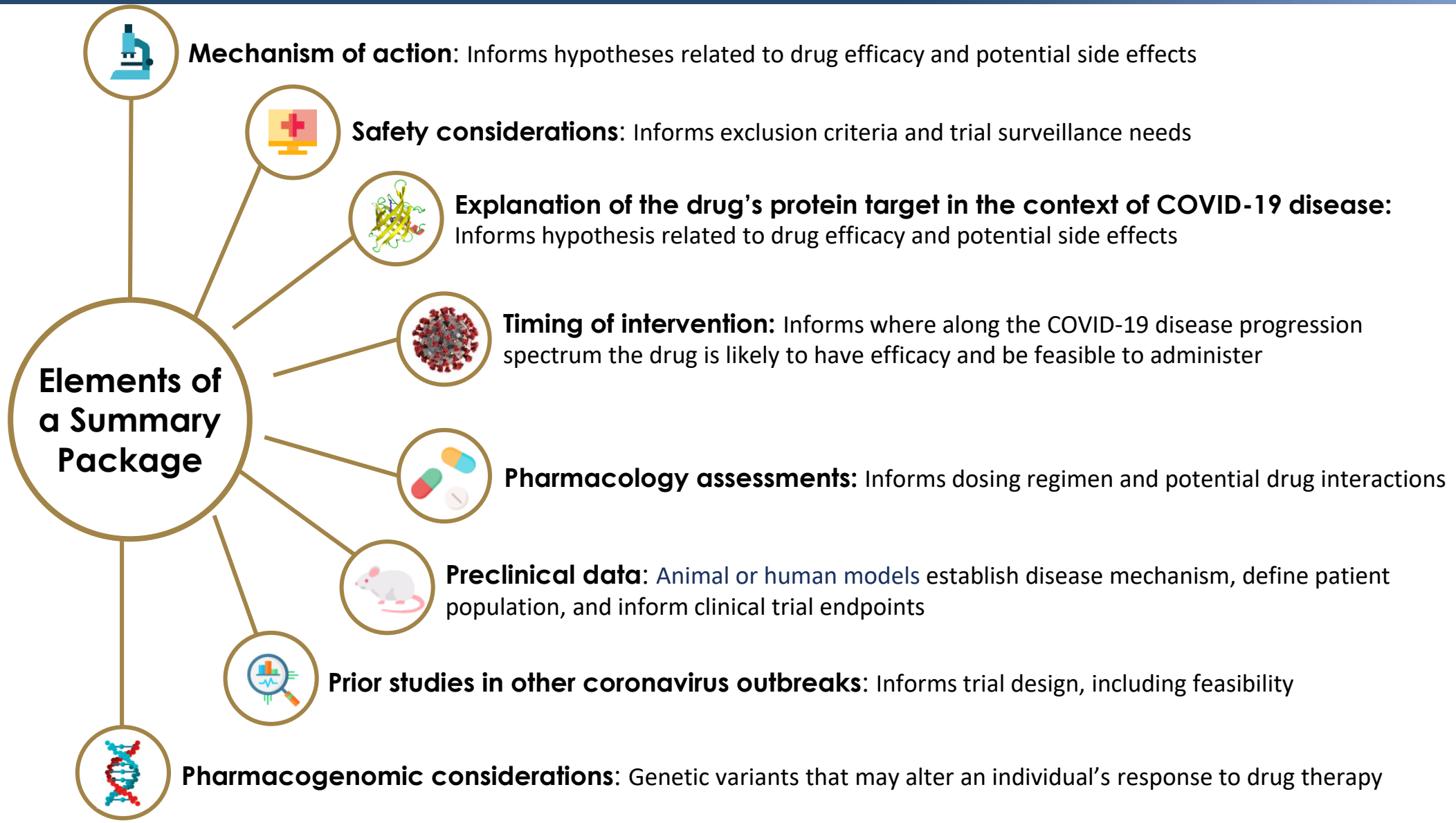




Standardized evidence summary

Expert voting

Science Unit Support of Agent Prioritization: Summary Packages



Mechanism of action: Informs hypotheses related to drug efficacy and potential side effects

Safety considerations: Informs exclusion criteria and trial surveillance needs

Explanation of the drug's protein target in the context of COVID-19 disease: Informs hypothesis related to drug efficacy and potential side effects

Timing of intervention: Informs where along the COVID-19 disease progression spectrum the drug is likely to have efficacy and be feasible to administer

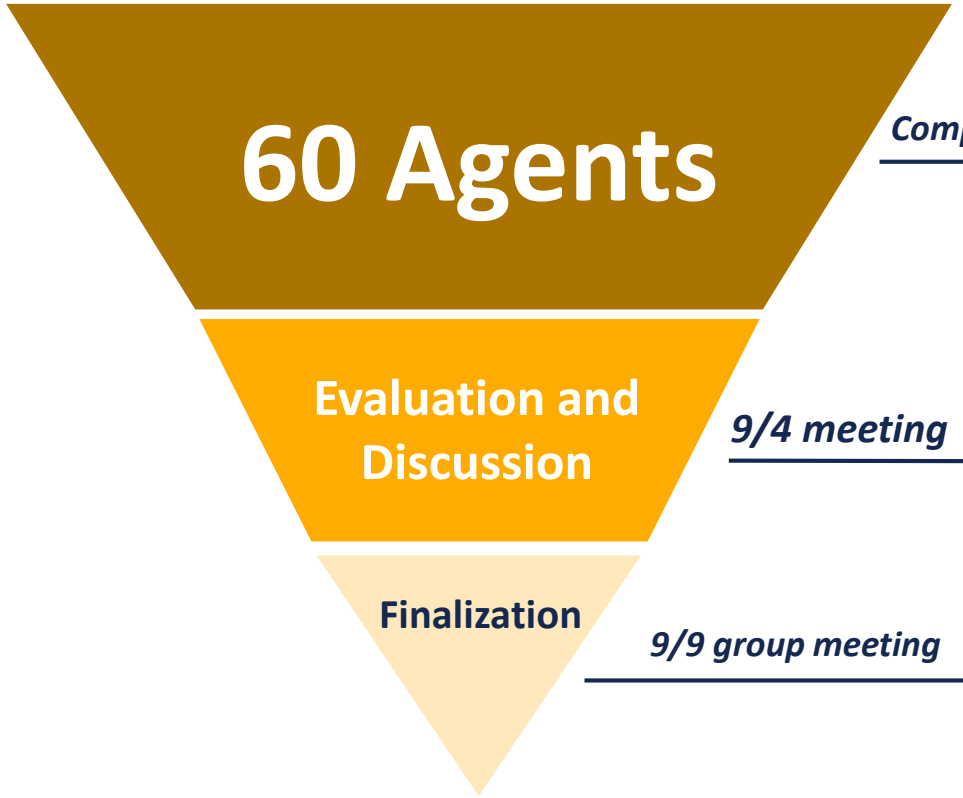
Pharmacology assessments: Informs dosing regimen and potential drug interactions

Preclinical data: Animal or human models establish disease mechanism, define patient population, and inform clinical trial endpoints

Prior studies in other coronavirus outbreaks: Informs trial design, including feasibility

Pharmacogenomic considerations: Genetic variants that may alter an individual's response to drug therapy

Process for Agent Prioritization:
Flow for filtering therapies into Master Protocols



Complete

Survey of Agent Prioritization Committee

- One-pagers grouped, reviewed and scored by therapeutic area (10-25 agents *per reviewer*) leveraging all nominated experts/NLHBI program.

9/4 meeting

Feasibility Assessment and Working Group Review

- Review of priority agents, confirming NHLBI interest, **non-redundancy with other trials**, and access to therapeutics
- Deeper dive detailed assessment packages provided to Working Groups

****current development is immunomodulatory and host tissue agents****

9/9 group meeting

Deliberation

- Therapeutic domain Working Groups will have live group discussion of candidates for further prioritization, producing candidates for recommendation to the Steering Committee

Recommendation to SC for Assignment to Master Protocol Arms

- Factor in practical and logistical details for each agent
- Assignment into master protocol arms based on common features

Final selected therapies will be incorporated into master protocols

Intervention features

- Type (e.g. small molecule, biologic, device, behavioral)
- Therapeutic domain/target host response
- Route of administration (e.g. IV, oral, inhaled)
- Disease phase where therapy is most likely to have efficacy
- Duration of intervention
- Safety profile (for eligibility criteria and monitoring)

Outpatient
Master Protocol

Inpatient
Master Protocol

Recovering
Master Protocol

Study Implementation

Sonia Thomas, DrPH

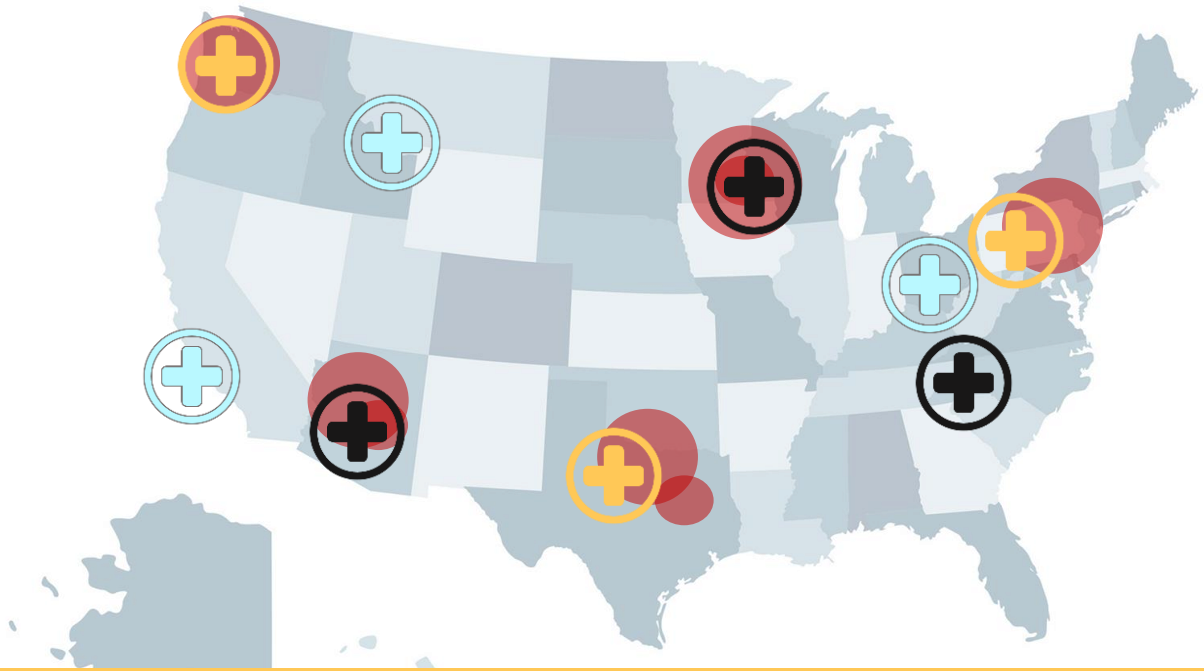
CONNECTS ACC PI

RTI International

Forming Study Implementation Teams

CONNECTS Participating DCCs

CONNECTS Participating Networks & Sites



Study Team Composition

Network A

Network B

Network C

Disease Activity

Team composition determined by expertise, site populations. Registered sites will be activated based on geographic distribution of disease activity.

Forming Study Implementation Teams

CONNECTS Participating DCCs

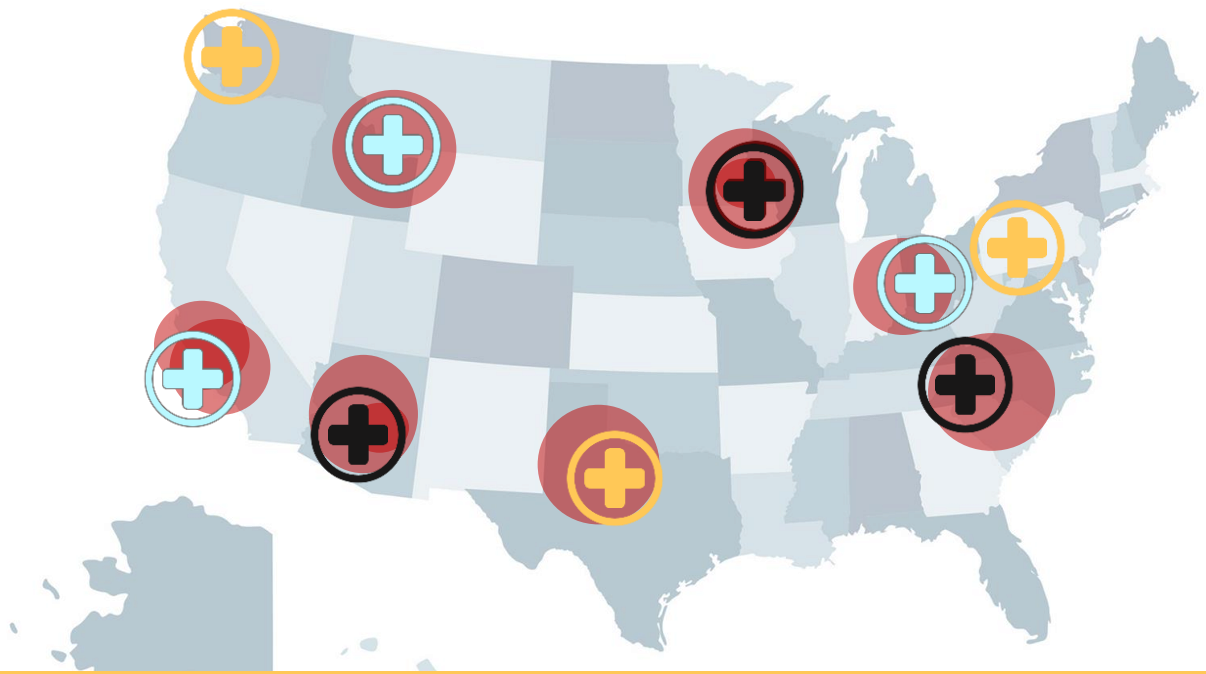
Network A

Network B

Network C

Disease Activity

CONNECTS Participating Networks & Sites



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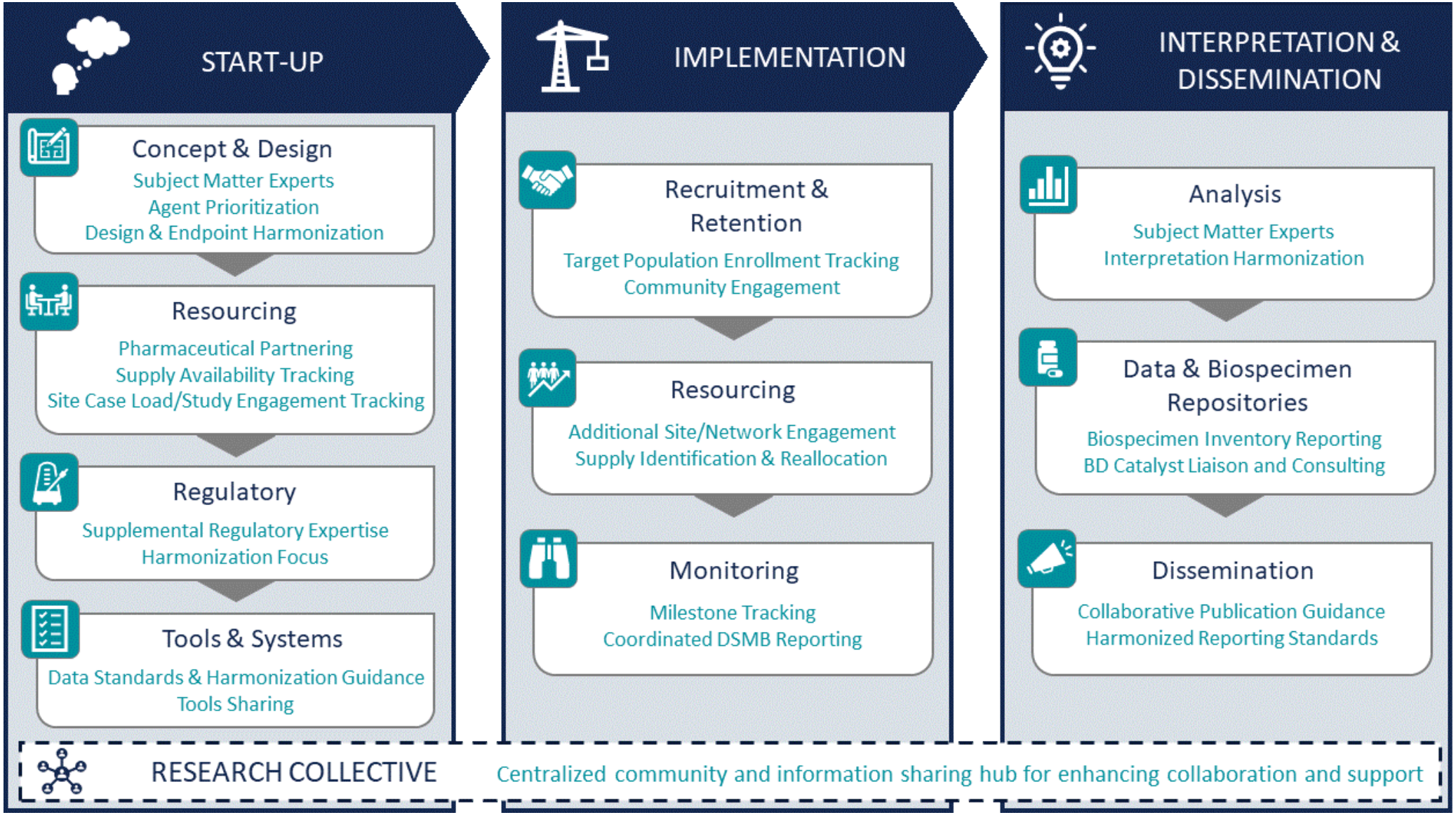
Study Team Composition

ACC: Supporting CONNECTS Studies



Common Data Elements (CDE) Principles

- **Principle 1: Build on existing trials**
  - Curate CDEs from protocols and CRFs of existing COVID-19 studies
- **Principle 2: Build on existing standards and NIH CDE resources**
  - Prioritize data elements in existing standards
- **Principle 3: Enable multiple types of analysis**
  - Across- and pooled- studies, epidemiological studies
- **Principle 4: Allow room for innovation**
  - Minimize CDE burden
  - Classify CDEs as “Core” or “Recommended”

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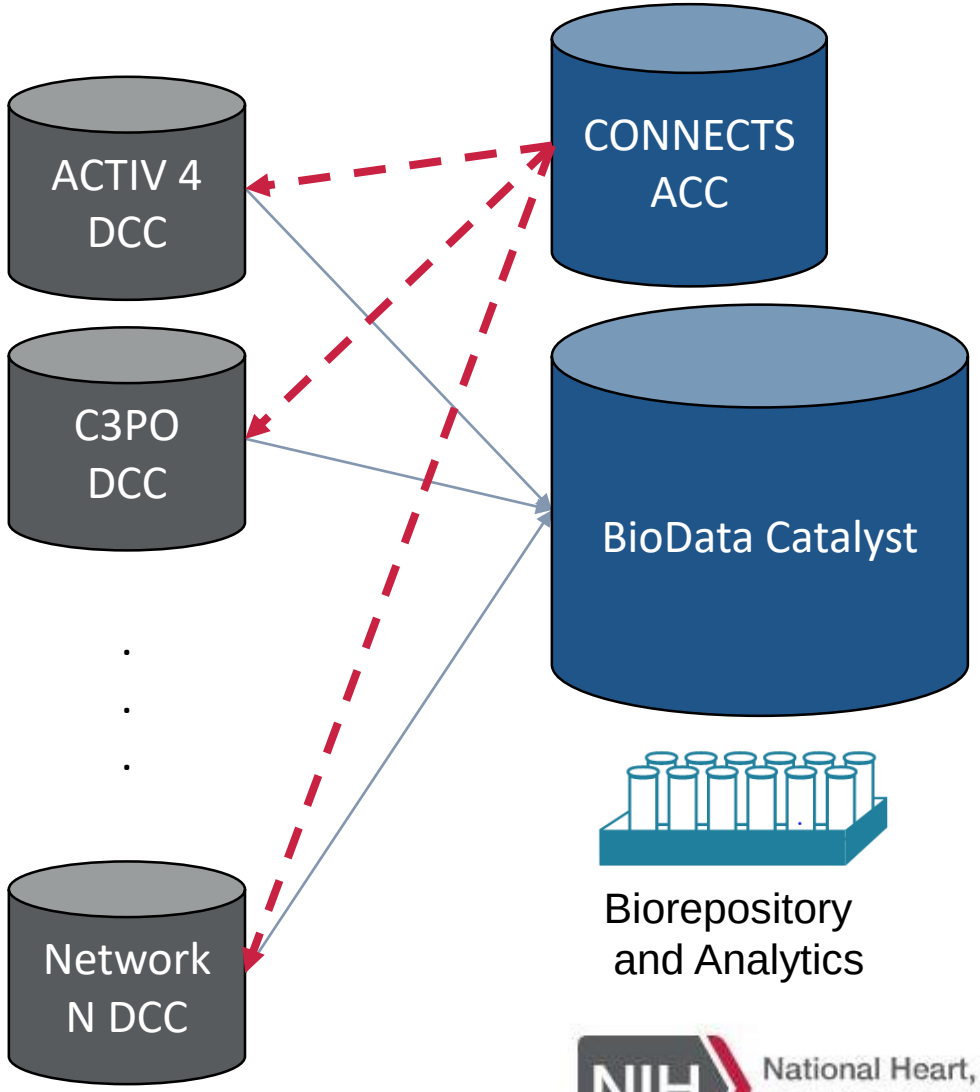
Common Data Elements and Data Transfer Activity

- **Common Data Element Manual**
  - What is measured
  - How it is measured and recorded
- **Review of draft protocols and CRF**s
- **Up-front data transfer planning and coordination**
  - To ACC for study enrollment dashboard and Biorepository Database
  - To BioData CATALYST for data sharing

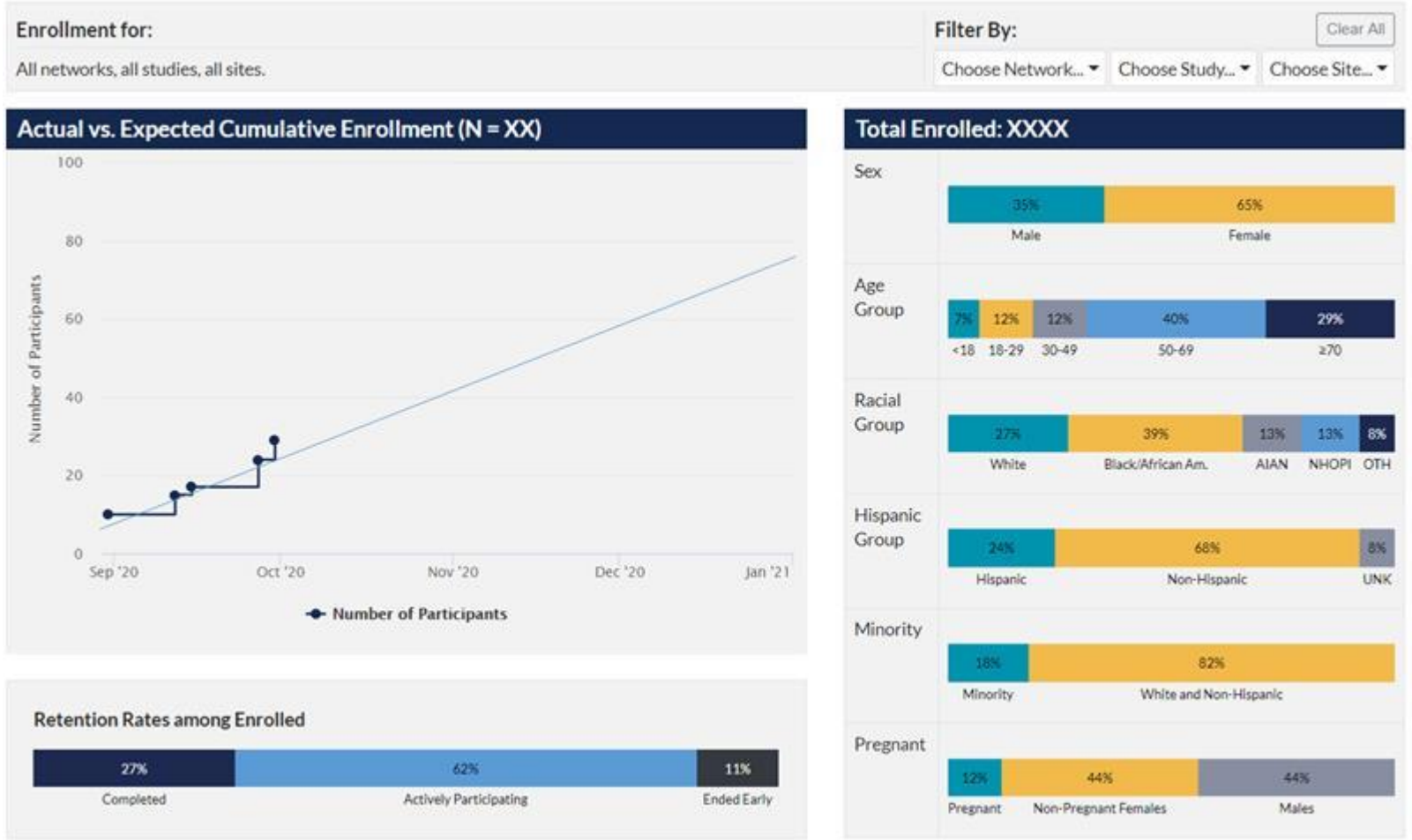


NIH National Heart, Lung, and Blood Institute | BioData CATALYST

NIH National Heart, Lung, and Blood Institute

Centralized Information Portal

- **Site ID tools**
  Map-based and searchable by network, by study, and by site characteristics
- **Study Enrollment**
  Real-time through data transfer from study DCC
- **Study Milestones**
  Efficient, seamless reporting to NHLBI



National Heart, Lung, and Blood Institute

Call for Sites!

- Regional Site Consortiums (networks of community hospitals)
- Sites in areas with projected hot-spots
- “Spoke sites” that can be led by teams from strong academic hubs
- Existing National/International consortiums

- Current need:
  - Inpatient, outpatient, and post-hospital recovering for anti-thrombotics
- Please email to both:

  activ4siteenroll@pitt.edu

  info@nhlbi-connects.org

ACTIV-4

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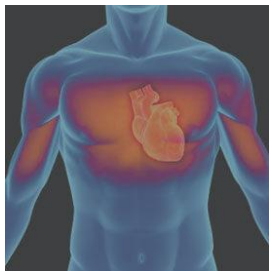

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