

# COVID-19 Update

## Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Therapeutics

Meeting of the NIH Advisory Committee to the Director

December 10, 2020

# Order of Presentations

## **Preclinical ACTIVE, ACTIV-1, and Inpatient Convalescent Plasma RCTs**

*Christopher P. Austin, M.D. (NCATS)*

## **ACTT, ACTIV-2, -3, -5, AND IVIg**

*H. Clifford Lane, M.D. (NIAID)*

## **ACTIV-4, Outpatient Convalescent Plasma RCTs, Community Engagement Alliance (CEAL) Against COVID-19 Disparities**

*Gary H. Gibbons, M.D. (NHLBI)*

## LAUNCH

On April 17, NIH announced the launch of a public-private partnership, **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)**

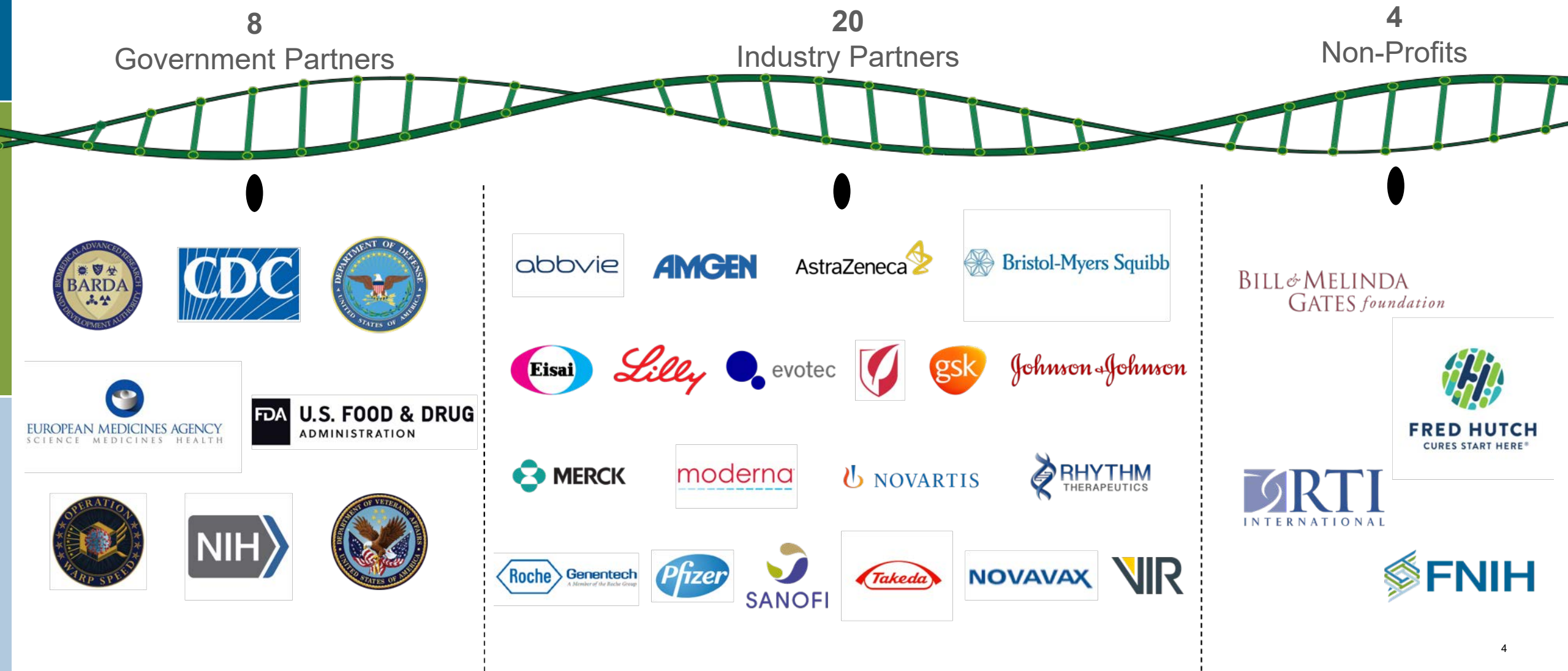
## MISSION

Develop a coordinated research response to **speed COVID-19 treatment and vaccine options**



# ACTIV Stakeholders

ACTIV is being coordinated by the Foundation for the National Institutes of Health (FNIH), and has brought together multiple partners from government, industry and non-profits.



# ACTIV Fast-Track Focus Areas | Objectives & Composition

The ACTIV partnership consists of four fast-track focus areas (Working Groups) with membership of both public and private sector representatives to oversee tactical operations :



	Vaccines	Preclinical	Clinical Trial Capacity	Therapeutics – Clinical
<b>Objective</b>	+ Accelerate the evaluation of vaccine candidates to enable rapid authorization or approval	+ Develop a collaborative, streamlined forum to identify preclinical treatments	+ Improve clinical trial capacity and effectiveness	+ Accelerate clinical testing of the most promising COVID treatments
<b>Sub-Groups</b>	+ Vaccines Clinical Trials + Protective Immune Responses + Vaccine-Associated Immune Enhancement	+ Animal Models + In Vitro Assays	+ Survey Development + Clinical Trial Network Inventory + Innovations	+ Agent Prioritization + Master Protocol

# Preclinical Working Group



## OBJECTIVE

Standardize and share preclinical evaluation methods and sharing testing resources in an open forum that allows for effective validation and comparison of therapeutic candidates.

## ACCOMPLISHMENTS TO DATE

- ✓ Developed a **master inventory of preclinical testing** resources
- ✓ Established SOPs for **accelerated preclinical agent development** in response to a pandemic
- ✓ **Developed a National Strategy for NHP Research** and a process to coordinate NHP studies centrally through NIH, and “field guides” for the use of small animal testing models
- ✓ Created and published online 9 “field guide” videos for use of small animal models in COVID-19 preclinical development
- ✓ Established a process for **prioritizing in vitro assays** and **evaluating preclinical compounds**
- ✓ Created a **public database** for sharing preclinical data (NCATS Open Science Portal)
- ☐ **Conducting a “matchmaking” process** to pair promising compounds with available preclinical resources and funding, on an ongoing basis
- ☐ **Assess the impact of emerging viral mutations on efficacy of vaccines and therapeutics**
  - ✓ *Completed*
  - ☐ *In progress*





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OpenData Browser

Assays

Animal Models

Omics Efforts

Highlights

Resources ▾

## Small Animals



Species	Modification	Model Name/Nomenclature	Vaccines	Antivirals	Neutralizing Antibodies	Other Therapies	Infectivity	Transmission	Disease Enhancement	Disease Manifestation & Pathology	Extent of disease
Ferret	Outbred Stock	Ferret	✓								
Guinea Pig	Wild Type	Guinea Pig									
Hamster	Inbred Strain	Syrian Golden	✓								
Hamster	Transgenic	Tg(K18-hACE2)									
Mouse	ACE2 Transduced	Adenovirus transduced hACE2	✓								
Mouse	Inbred Strain	BALB/c (adapted virus)	✓								
Mouse	Knock-In	C57BL/6-Ace2 <sup>em1</sup> (ACE2) <sup>Yowa</sup>	✓								
Mouse	Transgenic	B6.Cg-Tg(K18-ACE2)2PrImn/J	✓								

## Non-Human Primates



Species	Geographic Origin	Route of Exposure	Vaccines	Antivirals	Neutralizing Antibodies	Other Therapies	Infectivity	Transmission	Disease Enhancement	Disease Manifestation & Pathology	Extent of disease
African Green	St. Kitts (wild-caught)	Intratracheal/intranasal, aerosol	✓		✓		Y	TBD	TBD	Lung lesions; interstitial pneumonia; recovery	Mild to moderate
Aged African Green	St. Kitts (wild-caught)	Intratracheal/intranasal, intratracheal, aerosol	✓		✓		Y	TBD	TBD	Lung lesions; interstitial pneumonia; cytokine storm; ARDS; varied death and recovery	Severe
Cynomolgus macaque	Cambodia	Intratracheal/intranasal, intratracheal	✓	✓	✓		Y	TBD	TBD	Lung lesions; interstitial pneumonia; recovery	Mild
Rhesus macaque	China or India	Intratracheal/intranasal, intratracheal, ocular, oral, aerosol	✓	✓	✓		Y	TBD	TBD	Lung lesions; interstitial pneumonia; recovery	Mild

# Clinical Trial Capacity Working Group

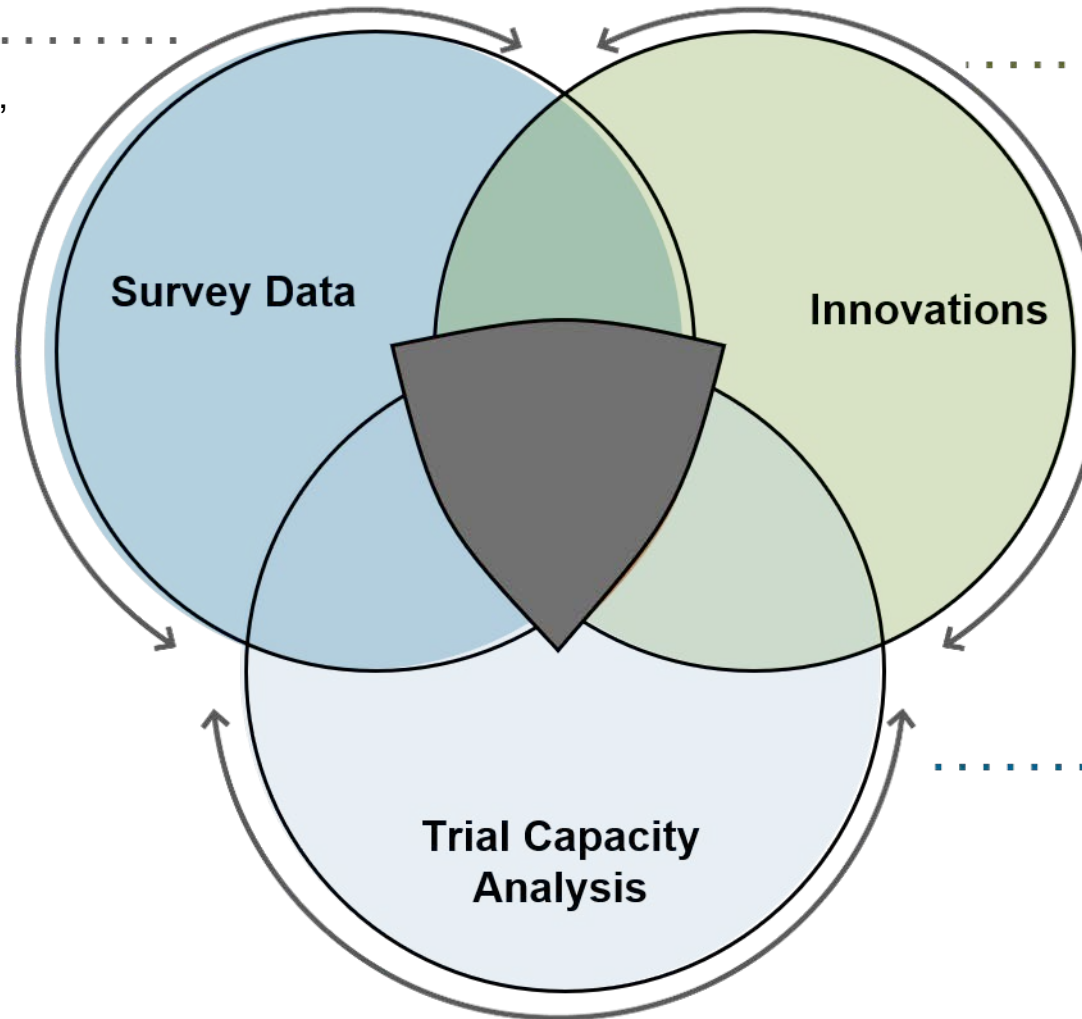
The Working Group developed an inventory of clinical trial capacity, including networks of NIH ICs, industry, and other organizations, that will serve as a guide for how and where to implement effective COVID-19 clinical trials.

- ✓ **3** unique clinical trial capacity surveys developed for **Networks, Sites, and Clinical Research Organizations (CROs) and Site Management Organizations (SMOs)**

- ✓ **63 Networks** completed the survey\*

- ✓ **725 total Sites** completed the survey\*

- ✓ **39 CROs/SMOs** completed the survey\*



- ✓ **Identified 52 novel and scalable enhancements / efficiencies** for therapeutic clinical protocols and vaccine protocols

- ✓ **A Tableau-based dashboard** was created to query and visualize survey data

- ✓ Clinical Trial network, site, and CRO/SMO survey data is combined **in one comprehensive view**

- ✓ **Dashboard includes overlay of COVID-19 infection data** with collected survey data to inform decisions around optimizing site selection for therapeutic and vaccine trials



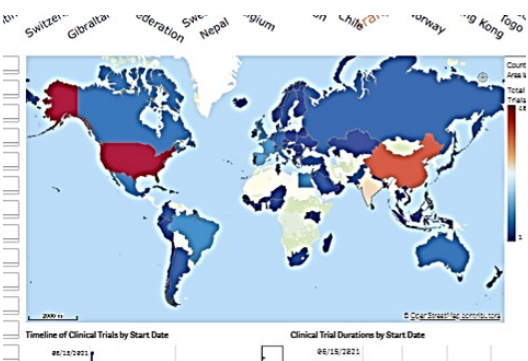
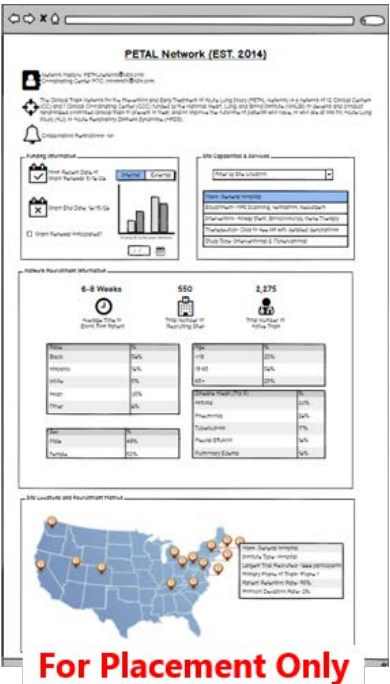
# TransNIH 2: Bringing Clinical Trial Networks Together

## Clinical Trial Network Inventory

- Central repository of NIH clinical trial network information for improved response planning to current and future pandemics and health threats

### Highlights

- Coordination with OER and NIAID
- Jump-started ACTIV Clinical Trial Capacity Working Group and rapid identification of sites and special populations



## COVID-19 Clinical Trials “Data Lake”

- Curated database combining information from several large clinical trial registries to provide a unified view of the global clinical trials landscape for COVID-19

### Highlights

- Successful transfer of system from Operation Warp Speed to NCATS

# TransNIH 8: Preclinical Therapeutic Discovery

## COVID-19 NIH Intramural Program Inventory Dashboard

Version 1.0 – Built in

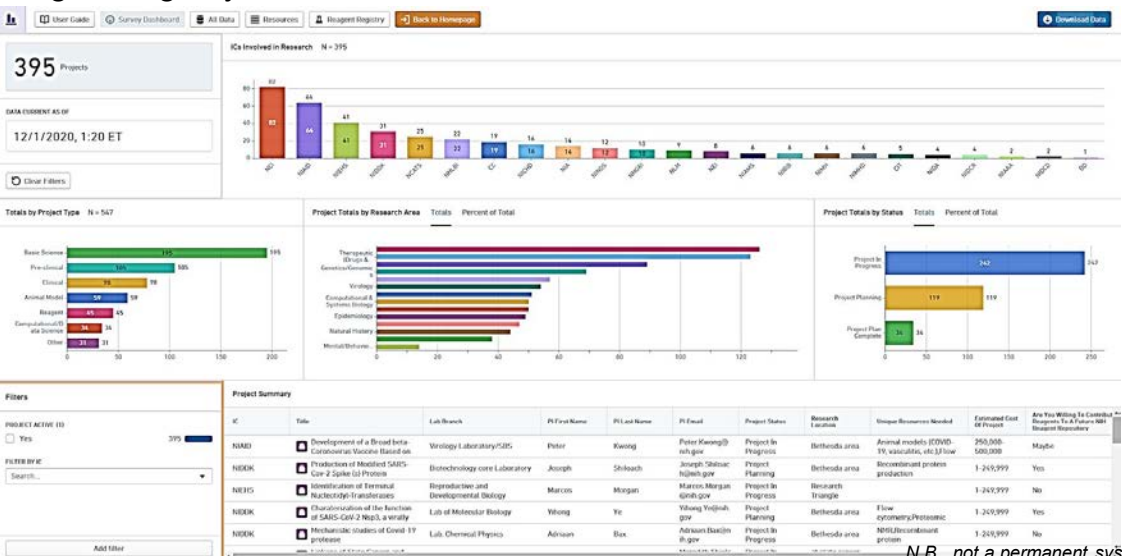
April with the COVID SIG, included forms to collect information that populates a visualization

dashboard – primarily, project dashboard & reagent registry

Stakeholder user interviews

Version 2.0 – Rolled out in Nov

- Enable updating of IRP entries and establish cadence of updating projects
- Improve search and data extraction functionality
- Improve dashboard layout and user instructions to make more user friendly



N.B., not a permanent system

## Review & Prioritization Activities

The WG members have gone through **2 rounds of project reviews** to date, reviewing all **370 projects** in the 1.0 dashboard. The first review cycle occurred in May; the second occurred in July. To date, 32 projects have been prioritized.

# Therapeutics – Clinical Working Group



## OBJECTIVE

Prioritize promising therapeutic candidates and accelerate their clinical evaluation by establishing large-scale master protocol trials.

## ACCOMPLISHMENTS TO DATE

- ✓ Developed and continuously enhanced a **world-class process for prioritizing clinical agents** for rapid testing
- ✓ Evaluated ~500 available agents with potential relevance for COVID-19 therapies and **prioritized the most promising agents for further study** (agent prioritization continues on a rolling basis)
- ✓ **Assessed, designed, and harmonized seven master protocols** for ACTIV clinical trials, focusing on candidates selected through the agent prioritization process
- ✓ **Selected clinical trial networks** best suited to execute these master protocols and supported NIH efforts to launch them; **six protocols have been launched to date**
- ❑ **Actively working with NIH and OWS across all protocols to ensure they are effectively coordinated, efficiently managed, and meet recruitment targets**

✓ *Completed*

❑ *In progress*

# Current Portfolio of ACTIV Master Protocols

ACTIV Therapeutics has been taking a portfolio approach to address the dramatic health and economic challenges posed by the pandemic, with harmonized “master protocol” trials.

## DESIRED OUTCOMES

## STATUS



### ACTIV-1

- Phase III trial of 3 host-targeted immune modulators
- Inpatient (hospitalized) patient population
- NCATS Trial Innovation Network + CRO

- **Trial launched October 16**
- First 3 agents selected – Abatacept, Infliximab, and Cenicriviroc

### ACTIV-2

- Phase II/III trial of up to 5-7 Neutralizing Antibodies and Oral Antivirals
- Outpatient population
- NIAID ACTG network + CRO

- **Trial launched August 3**
- Initial agent: nAb from Lilly; onboarding other agents

### ACTIV-3

- Phase III trial of 5-7 Neutralizing Antibodies and Oral Antivirals
- Inpatient population
- NIAID INSIGHT + NHLBI PETAL + NHLBI CSTN + VA networks +CRO

- **Trial launched August 4**
- Initial agent: nAb from Lilly (halted for futility Oct. 26); onboarding other agents
- Preliminary results submitted to NEJM on Nov 9

### ACTIV-4

- Phase III trial of anticoagulants (heparin, aspirin) and antiplatelet drug
- Three different populations: pre-hospitalized, hospitalized, & post-hospitalized
- NHLBI-NINDS CONNECTS network

- **Hospitalized and Pre-Hospitalized cohorts launched on Sept 17**
- **Post-hospitalized cohort launching early December**
- First agents – LMWH and UFH (hospitalized) and low dose aspirin, high dose aspirin, and apixaban (pre-hospitalized)

### ACTIV-5 (Big Effect Trial)

- Phase II “proof of concept” study to identify multiple promising treatments
- Inpatient population
- NIAID networks + CRO

- **Trial launched October 12**
- Two initial agents selected – Risankizumab + Lenzilumab
- Prioritizing additional agents

# ACTIV-1: Immunomodulators

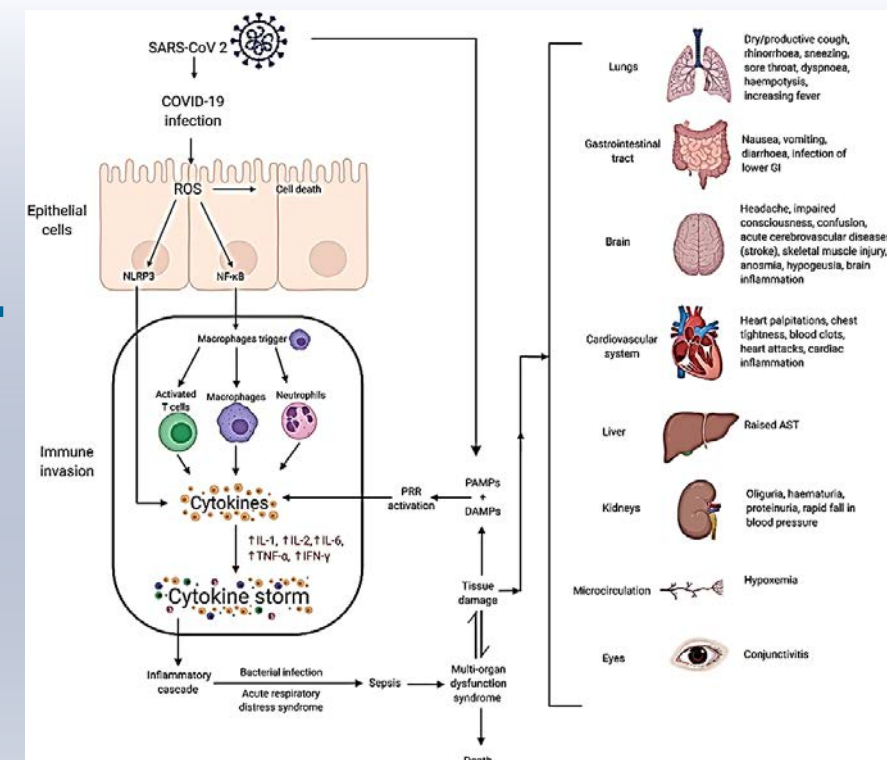
NCATS CTSA Trial Innovation Network/Hubs + CRO  
*Launched October 16, 2020*

**Design:** Randomized, placebo-controlled adaptive master protocol trial

**Patient population:** Moderately or severely ill hospitalized patients with COVID-19 cytokine storm

**Recruitment goal:** 2200

**Sites:** 15 active, expanding to 50



## INITIAL STUDY AGENTS

- Infliximab (Remicade): anti-TNFα mAb
- Abatacept (Orencia): CTLA-4-Ig fusion protein
- Cenicriviroc (CVC): SM CCR2/CCR5 antagonist

## OUTCOME MEASURES

- 1°: Time to Recovery by Day 29
- 2°: Clinical Status on day 15 & Day 29 defined by 8-point ordinal scale
- 2°: Mortality

# NCATS Convalescent Plasma RCTs

## *Multisite trials run through CTSA network*

- Two independent but coordinated trials, begun in April and expanded in August
- Patient population: **inpatients** early in disease course
- Intervention: 1 unit **high-titer convalescent plasma** vs crystalloid placebo
- Outcomes: **improvement on ordinal scale**, hospitalization duration, mortality
- Enrollment targets: 1000 participants in each trial (**total enrollment = 2000**)
- **CONTAIN COVID-19** (NCT04364737)
  - Current sites = 8, expanding to 14 as needed
    - **NYU, Einstein**, Milwaukee, Iowa, Michigan, Univ Illinois Chicago, Johns Hopkins, Oregon
  - Current total enrollment (as of December 4): **546**
- **PassItOnII** (NCT04362176)
  - Current sites = 14, expanding to 30 as needed
    - **Vanderbilt**, Univ Colorado Denver, Univ Utah, Univ Mississippi, Our Lady of the Lake (Baton Rouge, LA), Univ Washington, Newton-Wellesley Hospital, Univ Minnesota, Univ Kansas, State Univ New York Buffalo, Virginia Commonwealth Univ, Scripps Research Institute, Univ Maryland, Ohio State Univ
  - Current total enrollment (as of December 4): **297**



*Supported with NCATS CURES and Operation Warp Speed funds*