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 ACTIV, ACTIV-1, and Inpatient Convalescent Plasma RCTs
Christopher P. Austin, M.D. (NCATS)

ACTT, ACTIV-2, -3, -5, and IVlg
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)
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.

- **8** Government Partners
- **20** Industry Partners
- **4** Non-Profits
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:

**Objective**
- Vaccines: Accelerate the evaluation of vaccine candidates to enable rapid authorization or approval
- Preclinical: Develop a collaborative, streamlined forum to identify preclinical treatments
- Clinical Trial Capacity: Improve clinical trial capacity and effectiveness
- Therapeutics – Clinical: Accelerate clinical testing of the most promising COVID treatments

**Sub-Groups**
- 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**

FNIH

✓ **Completed**  ❏ **In progress**
### Small Animals

<table>
<thead>
<tr>
<th>Species</th>
<th>Modification</th>
<th>Model Name/Nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferret</td>
<td>Outbred Stock</td>
<td>Ferret</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>Wild Type</td>
<td>Guinea Pig</td>
</tr>
<tr>
<td>Hamster</td>
<td>Inbred Strain</td>
<td>Syrian Golden</td>
</tr>
<tr>
<td>Hamster</td>
<td>Transgenic</td>
<td>Tg(K18-hACE2)</td>
</tr>
<tr>
<td>Mouse</td>
<td>ACE2</td>
<td>Adenovirus transduced hACE2</td>
</tr>
<tr>
<td>Mouse</td>
<td>Inbred Strain</td>
<td>BALB/c (adapted virus)</td>
</tr>
<tr>
<td>Mouse</td>
<td>Knock-In</td>
<td>C57BL/6-JACE2&lt;sup&gt;TM&lt;/sup&gt;/JACE2/Yova</td>
</tr>
<tr>
<td>Mouse</td>
<td>Transgenic</td>
<td>B6.Cg-TgK18-ACE2&lt;sup&gt;TM&lt;/sup&gt;/PimvJ</td>
</tr>
</tbody>
</table>

### Non-Human Primates

<table>
<thead>
<tr>
<th>Species</th>
<th>Geographic Origin</th>
<th>Route of Exposure</th>
<th>Vaccine</th>
<th>Antibody</th>
<th>Neutralizing Antibodies</th>
<th>Other Therapy</th>
<th>Transmission</th>
<th>Disease Manifestation &amp; Pathology</th>
<th>Extent of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Green</td>
<td>St. Kitts (wild-caught)</td>
<td>Intratracheal/intranasal, aerosol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Lung lesions; interstitial pneumonia; recovery</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Aged African Green</td>
<td>St. Kitts (wild-caught)</td>
<td>Intratracheal/intranasal, intratracheal, aerosol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Lung lesions; interstitial pneumonia; cytokine storm; ARDS; varied death and recovery</td>
<td>Severe</td>
</tr>
<tr>
<td>Cynomolgus Macaque</td>
<td>Cambodia</td>
<td>Intratracheal/intranasal, intratracheal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Lung lesions; interstitial pneumonia; recovery</td>
<td>Mild</td>
</tr>
<tr>
<td>Rhesus Macaque</td>
<td>China or India</td>
<td>Intratracheal/intranasal, intratracheal, ocular, oral, aerosol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Lung lesions; interstitial pneumonia; recovery</td>
<td>Mild</td>
</tr>
</tbody>
</table>
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.

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

- 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*

- Survey Data

- Innovations

- Trial Capacity Analysis

- 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

*Additional organizations will be surveyed as identified
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

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

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.

N.B., not a permanent system
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

FNIH ✔  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

#### ACTIV-1
- Phase III trial of 3 host-targeted immune modulators
- Inpatient (hospitalized) patient population
- NCATS Trial Innovation Network + CRO

#### ACTIV-2
- Phase II/III trial of up to 5-7 Neutralizing Antibodies and Oral Antivirals
- Outpatient population
- NIAID ACTG network + CRO

#### ACTIV-3
- Phase III trial of 5-7 Neutralizing Antibodies and Oral Antivirals
- Inpatient population
- NIAID INSIGHT + NHLBI PETAL + NHLBI CSTN + VA networks + CRO

#### ACTIV-4
- Phase III trial of anticoagulants (heparin, aspirin) and antiplatelet drug
- Three different populations: pre-hospitalized, hospitalized, & post-hospitalized
- NHLBI-NINDS CONNECTS network

#### ACTIV-5
- Phase II “proof of concept” study to identify multiple promising treatments
- Inpatient population
- NIAID networks + CRO

### STATUS

#### ACTIV-1
- **Trial launched October 16**
- First 3 agents selected – Abatacept, Infliximab, and Cenicriviroc

#### ACTIV-2
- **Trial launched August 3**
- Initial agent: nAb from Lilly; onboarding other agents

#### ACTIV-3
- **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
- **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
- **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

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**INITIAL STUDY AGENTS**

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

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**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