Gary H. Gibbons, M.D.
Director
National Heart, Lung, and Blood Institute

122nd Meeting of the Advisory Committee to the Director
June 10, 2021
NHLBI-NIH Strategic Approach to Addressing COVID-19

**Goals**

- Reduce case severity/fatality, speed recovery
- Understand short- and long-term trajectory
- Enable risk stratification, precision interventions
- Identify biomarkers and therapeutic targets
- Target populations most severely affected

**Host-Directed Therapeutics Clinical Trials**

**Observational/Longitudinal Studies**

**Translational/Pre-Clinical Studies**

**Data Resources and Platforms**

**Community-Engaged Research**
NHLBI’s “Network of Networks” (CONNECTS): Integration into the NIH ACTIV Trial Infrastructure

Goal: Leverage and expand NHLBI’s national clinical research networks to rapidly and nimbly respond to emerging research and clinical needs for COVID-19

- Leverages existing assets, data, and studies
- Creates a comprehensive, expandable platform that links trial network, registries, and cohorts
- Facilitates case finding, clinical trial accrual, and community engagement
Can colchicine prevent complications due to inflammation in outpatients?

**Patient Populations**
- Non-hospitalized patients
- 40 years old and older
- At least one high-risk characteristic

**Anti-Inflammatory**
- Colchicine or placebo for 30 days

Primary Endpoint of Hospitalization or Death

<table>
<thead>
<tr>
<th>Colchicine (n=2075)</th>
<th>Placebo (n=2084)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td>96 (4.6%)</td>
<td>126 (6.0%)</td>
<td>0.75 (0.57–0.99)</td>
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Benefit of colchicine observed among outpatients with confirmed COVID-19

Published in *The Lancet*
Hydroxychloroquine was promoted as a COVID-19 treatment but lacked safety and efficacy data.

**Patient Populations**
- Adults hospitalized with respiratory symptoms
- Median age 57 years
- 37% Hispanic; 23% Black

**Anti-Inflammatory**
- Hydroxychloroquine or placebo

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**Survival and Hospital Discharge Following Randomization**

- Hydroxychloroquine treatment demonstrated no benefit or harm to COVID-19 inpatients

*Published in JAMA*
Convalescent Plasma Treatment for Outpatients with COVID-19: C3PO Trial

Seek low-cost options for outpatients at risk for severe COVID-19: few RCTs with CP for other illnesses

**Patient Populations**
- ED patients with mild to moderate symptoms for ≤1 week
- ≥1 risk factor associated with severe COVID-19

**Passive Immunity**
- Single dose of convalescent plasma or
- Saline placebo

*Interim analysis found convalescent plasma has no significant benefit or harm; study enrollment stopped early*

Registered with ClinicalTrials.gov: NCT04355767
Antithrombotic Strategies to Prevent COVID-19 Complications in Hospitalized Patients: ACTIV-4A

Blood clots and inflammation are common complications in COVID-19 patients.

**Patient Population**
- Hospitalized patients
- Stratified by severe or moderate illness

**Anti-Thrombotic**
- **Therapeutic dose** of heparin
- **Prophylactic dose** of heparin

**Therapeutic dose of anticoagulant helps moderately ill but not critically ill inpatients**

The ATTACC, ACTIV-4a, and REMAP-CAP Investigators. medRxiv 2021.05.13.21256846; doi: https://doi.org/10.1101/2021.05.13.21256846
Working Hypothesis: Imbalance in the Renin-Angiotensin-Aldosterone System (RAAS) Modulates COVID-19 Clinical Course

SARS-CoV-2 leads to host tissue injury, increases pro-inflammatory, pro-thrombotic and pro-fibrosis signaling.

Patient Populations

Hospitalized Patients

Tissue Injury Repair

ACTIV – 4 RAAS

Test whether RAAS targeting drugs can prevent severe COVID-19 responses including:

- Vascular Injury
- Pro-thrombotic
- Inflammatory
- Fibrotic

Adapted from Goldin et al., *Transl Med Commun.*, 2020 and Ingraham et al., *Eur Respir J.*, 2020
Evaluating Effectiveness of Antithrombotic and RAAS-Targeting Drugs to Reduce Life-Threatening Complications

Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 (ACTIV-4)

COVID-19 Progression
- PREVENTION
- ASYMPTOMATIC
- SYMPTOMATIC
- ED
- HOSPITAL
- ICU
- RECOVERY
- RECOVERED

Patient Populations
- Pre-hospital Outpatient
- Hospitalized Patients
- Post-hospital Convalescent Patients

Anti-Thrombotic
- ACTIV – 4B
  - Anticoagulation (apixaban)
  - Antiplatelet agent: aspirin
  - Placebo

- ACTIV – 4A
  - Prophylactic dose of heparin
  - Therapeutic dose heparin

- ACTIV – 4C
  - Prophylactic dose anticoagulant
  - Therapeutic dose anticoagulant

Tissue Injury Repair
- ACTIV – 4 RAAS
  - Renin-angiotensin-aldosterone system targeting drugs
### NHLBI-NIH COVID-19 Rapid Adaptive Clinical Trials of Therapeutics: Impact on Clinical Practice

<table>
<thead>
<tr>
<th>Month</th>
<th>ORCHID Hydroxychloroquine</th>
<th>COLCORONA Colchicine</th>
<th>C3P0 – Convalescent Plasma</th>
<th>ACTIV – 4A (Severe Illness) Heparin</th>
<th>ACTIV – 4A (Moderate Illness) Heparin</th>
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NIH Ecosystem Addressing COVID-19 Clinical Challenges: Accelerating COVID-19 Therapeutic Interventions

Thank you to Patients, NIH Staff, Researchers for advancing COVID-19 therapies