NIH ACTIV THERAPEUTICS CLINICAL TRIALS

I. Overview and Updates
II. Host Tissue-Directed Therapeutics

NIH Advisory Council to the Director Briefing

December 9, 2021
Rising to the Public Health Challenges of COVID-19 and Beyond: Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

- Unparalleled public-private partnership
- Collaborative forum to identify most promising interventions and accelerate clinical testing
  - Launch and open sharing of master protocols for evaluating candidates
  - Improve clinical trial capacity/effectiveness by leveraging infrastructure and expertise from across NIH and non-NIH networks and CROs
- Accelerate evaluation of vaccine candidates to enable rapid authorization or approval
- Identify emerging variants and coordinate data sharing (TRACE WG)
- Unprecedented data sharing between academia and industry

VISIONARY LEADERSHIP

Providing partnership, dedication, and support to ACTIV Therapeutic Clinical Enterprise

Francis Collins, M.D., Ph.D.
Paul Stoffels, M.D.

ACTIV enterprise provides pathway and model for future preparedness efforts
NIH ACTIV THERAPEUTICS CLINICAL TRIALS: AT-A-GLANCE

**Enrollments & Activation**

- **13,813 Patients** enrolled into ACTIV trials
- **700+ Sites** in partnership with **multiple networks** including ACTG, CONNECTS, DCRI, INSIGHT, PETAL, CTSN, PCORnet, CTSA, IDEAS Sites, ACTT, and others

**Publications**

- **17 Scientific Publications** on ACTIV Trials released in **7 Medical Journals**
- These publications have been cited **478 times** (Google Scholar)

**Agent Reviews & Authorizations**

- **800+** Total agents reviewed by ACTIV Tx-Clinical and CONNECTS WGs Agent Review Panels
- **15** Agents fully enrolled and completed testing through the ACTIV Master Protocols
- **4** Agents proven efficacious against COVID-19 in analysis of data from ACTIV Trials. Other priority agents being tested

**EUA Achievements:**

- Lilly monoclonal approval
- Brii Bio rolling submission
- AZ applying for EUA intending to have ACTIV outpatient data noted in the submission package
- Both the **Merck and Pfizer compounds** being assessed for EUA were originally selected for testing in ACTIV trials
- ACTIV-4 work on heparin and other anticoagulants **changed clinical practice**
<table>
<thead>
<tr>
<th>Master Protocol</th>
<th>Protocol Description</th>
<th>Current Trial Status</th>
</tr>
</thead>
</table>
| ACTIV-1         | • Inpatient, RCT, Double-blind Phase III Master Protocol  
• Host-targeted Immune Modulators  
• NCATS TIN + DCRI + TRI + CRO  
• Target Sample Size (Patients per Arm): 540 | Trial launched on October 16, 2020  
• Agent(s) being tested: Abatacept, Cenicriviroc, Infliximab |
| ACTIV-2         | • Outpatient, RCT, Double-blind Phase II/III Master Protocol  
• Neutralizing Monoclonal Antibodies (nMABs) and Oral Antivirals  
• NIAID ACTG + CRO  
• Target Sample Size (Patients per Arm): 110 [Phase II] & 600 [Phase III] | Trial launched on August 3, 2020  
• Agent(s) being tested: nMABs (Lilly, Brii Bio, RU-BMS), IFN-beta (Synairgen), camostat (Sagent), nPAB (SAB) |
| ACTIV-3         | • Inpatient, RCT, Double-blind Phase III Master Protocol  
• Neutralizing Monoclonal Antibodies and other (e.g., protease inhibitor)  
• NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO  
• Target Sample Size (Patients per Arm): 500 | Trial launched on August 4, 2020  
• Agent(s) being tested: nMABs (Lilly, Brii, GSK-Vir, AZ), DARPin (Molecular Partners), protease inh. (Pfizer) |
| ACTIV-3B        | • Inpatient, RCT, Double-blind Phase III Master Protocol  
• Host-targeted Immune Modulators  
• NIAID INSIGHT + NHLBI PETAL + NHLBI CTSN + VA + CRO  
• Target Sample Size (Patients per Arm): 310 | Trial launched on April 21, 2021  
• Agent(s) being tested: Aviptadil (VIP) (NeuroRX)  
• Agents in the Pipeline: Immune Modulators for ARDS |
## NIH ACTIV THERAPEUTICS MASTER PROTOCOL DESCRIPTIONS

<table>
<thead>
<tr>
<th>Master Protocol</th>
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</table>
| **ACTIV-4A**    | • Inpatient, Pragmatic, Randomized, Open Label Phase III Master Protocol  
• Host-tissue Directed Therapeutics including Anticoagulants, Anti-platelet, other Anti-thrombotics  
• NHLBI CONNECTS Network  
• Target Sample Size (Patients per Arm): 1000 | **Trial launched on September 17, 2020**  
• Agent(s) being tested: LMWH, UFH, P2Y12 Inhibitors (Anti-platelet Agents); |
| **ACTIV-4B**    | • Outpatient, Randomized, Double-blind Phase III Master Protocol  
• Host-tissue Directed Therapeutics: Anticoagulants, Anti-platelet, other Antithrombotics  
• NHLBI CONNECTS Network  
• Target Sample Size (Patients per Arm): 1750 | **Trial launched on September 17, 2020**  
• Agent(s) being tested: Low-dose Aspirin, Prophylactic-dose Apixaban, Therapeutic-dose Apixaban |
| **ACTIV-4C**    | • Outpatient, Convalescent, RCT, Double-blind Phase III Master Protocol  
• Host-tissue Directed Therapeutics: Anticoagulants, Anti-platelet, other Antithrombotics  
• NHLBI CONNECTS Network  
• Target Sample Size (Patients per Arm): 2660 | **Trial launched on February 9, 2021**  
• Agent(s) being tested: Apixaban |
| **ACTIV-4HT**   | • Inpatient, Pragmatic, Randomized, Open Label Phase II/III Master Protocol  
• Host-tissue Targeted Therapies (Most focusing on RAAS Pathway Regulation)  
• NHLBI CONNECTS Network  
• Target Sample Size (Patients per Arm): 300+ | **Trial launched on July 2021**  
• Agent(s) being tested: TXA127, TRV027, Fostamatinib |
## NIH ACTIV THERAPEUTICS MASTER PROTOCOL DESCRIPTIONS

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<thead>
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| ACTIV-5         | • Inpatient, Randomized, Double-blind Phase II Master Protocol  
• Proof of Concept Study to Identify Promising Immuno Modulators  
• NIAID + CRO  
• Target Sample Size (Patients per Arm): 500 | **Trial launched on October 9, 2020**  
• Agent(s) being tested: Risankizumab, Lenzilumab, Danicopan |
| ACTIV-6         | • Outpatient, RCT, Double-blind Phase III Master Protocol  
• Existing Prescription and Over-the-counter Medications  
• NCATS + DCRI + PCORnet + SignalPath + CRO  
• Target Sample Size (Patients per Arm): 300 | **Trial launch on July 1, 2021**  
• Agent(s) being tested: Ivermectin, fluvoxamine, fluticasone |
<table>
<thead>
<tr>
<th>Status Summary of ACTIV Agents: Completed and Currently Under Study</th>
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</thead>
<tbody>
<tr>
<td><strong>ACTIV-I</strong></td>
</tr>
<tr>
<td>Enrolling But Not Yet Reviewed for Efficacy / Futility:</td>
</tr>
<tr>
<td>• Cenicriviroc</td>
</tr>
<tr>
<td>Ceased Enrollment (due to futility / low clinical value):</td>
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<tr>
<td>• Infliximab</td>
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<tr>
<td>• Abatacept</td>
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<tr>
<td>Continuing Enrollment (i.e., passed interim futility assessment):</td>
</tr>
<tr>
<td>• BMS-986414/BMS-986413</td>
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<tr>
<td>Completed Enrollment</td>
</tr>
<tr>
<td>• SNG001 IFN-beta</td>
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<tr>
<td>• LY-CoV-555</td>
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<tr>
<td><strong>ACTIV-2/2B</strong></td>
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<tr>
<td>• AZD7442 (IM)*</td>
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<tr>
<td>• AZD7442 (IV)*</td>
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<tr>
<td>• Camostat Mesylate</td>
</tr>
<tr>
<td>• BMS-986414/BMS-986413</td>
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<tr>
<td>• SAB-185</td>
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<tr>
<td>• Brii-196/Brii-198</td>
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<tr>
<td>• LY-CoV-555</td>
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<tr>
<td><strong>ACTIV-3/3B</strong></td>
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<tr>
<td>• Aviptadil and/or Remdesivir</td>
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<tr>
<td>• Pfizer PF-07304814</td>
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<tr>
<td>• LY-CoV-555</td>
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<tr>
<td>• Brii-196/Brii-198</td>
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<tr>
<td>• VIR-7831</td>
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<tr>
<td>• DARPin MP0420</td>
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<tr>
<td>• AZD7442 (IV) (awaiting topline data)</td>
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<tr>
<td><strong>ACTIV-4A</strong></td>
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<tr>
<td>• Therapeutic Heparin and P2Y12 Inhibitors in Moderately-ill Pts</td>
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<tr>
<td>• Prophylactic Heparin and P2Y12 Inhibitors in Critically-ill Pts</td>
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<tr>
<td>• Un-fractionated and Low Molecular Weight Heparin</td>
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<tr>
<td><strong>ACTIV-4B</strong></td>
</tr>
<tr>
<td>• Aspirin</td>
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<tr>
<td>• Apixaban</td>
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<tr>
<td><strong>ACTIV-4C</strong></td>
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<tr>
<td>• Apixaban</td>
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<tr>
<td><strong>ACTIV-4HT</strong></td>
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<tr>
<td>• TXA127</td>
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<tr>
<td>• TRV027</td>
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<tr>
<td>• Fostamatinib</td>
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<tr>
<td><strong>ACTIV-5</strong></td>
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<tr>
<td>• Danicopan</td>
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<tr>
<td>• Lenzilumab</td>
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<tr>
<td>• Risankizumab (awaiting topline data)</td>
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<tr>
<td><strong>ACTIV-6</strong></td>
</tr>
<tr>
<td>• Fluvoxamine</td>
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<tr>
<td>• Fluticasone</td>
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<tr>
<td>• Ivermectin</td>
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</tbody>
</table>

*Enrollment ceased at company’s request
Denotes agent lack of efficacy
Denotes proven agent efficacy
NIH ACTIV CLINICAL TRIALS TARGETING STAGES OF DISEASE

Severity of illness

No Illness

Stage I
(Early infection; Outpatient; ~80% patients)

Viral response phase

Stage II
(Pulmonary phase; Host-tissue injury; Inpatient; ~15% patients)

Host inflammatory and Host-tissue response phase

Stage III
(Hyperinflammation phase; Host-tissue injury; Inpatient ICU; ~5% patients)

Post Illness

Clinical signs and symptoms

No Infection

Infected; Not Hospitalized (With or without limitations)

Hospitalized; (No active medical problems → On O₂)

Hospitalized; (High Flow O₂ → Mechanical Ventilation)

Death

Convalescence

Potential Master Protocol

ACTIV-2, ACTIV-4b, ACTIV-6

ACTIV-1, ACTIV-3, ACTIV-3b ACTIV-4a, ACTIV-4 Host Tissue, and ACTIV-5

ACTIV-4c

Iterative learning process: Determining which therapeutic strategies work/don’t work in which clinical setting/stage of disease/patient group
NIH ACTIV CLINICAL TRIALS TARGETING STAGES OF DISEASE

Severity of illness

Stage I
(Early infection; Outpatient; ~80% patients)

Viral response phase

Stage II
(Pulmonary phase; Host-tissue injury; Inpatient; ~15% patients)

Stage III
(Hyperinflammation phase; Host-tissue injury; Inpatient ICU; ~5% patients)

20% Patients progress to moderate/severe disease requiring hospitalization

Post Illness

Clinical signs and symptoms

No Illness

No Infection

Infected; Not Hospitalized (With or without limitations)

Hospitalized; (No active medical problems → On O₂)

Hospitalized; (High Flow O₂ → Mechanical Ventilation)

Death

Convalescence

Potential Master Protocol

ACTIV-2, ACTIV-4b, ACTIV-6

ACTIV-1, ACTIV-3, ACTIV-3b, ACTIV-4a, ACTIV-4 Host Tissue and ACTIV-5

ACTIV-4c

- Majority (~80%) of SARS-CoV-2 infected patients experience mild to moderate symptoms resolving w/in 6–10 days
- ~20% of patients develop severe illness w/ typical interstitial bilateral pneumonia and ARDS; associated w/high fatality rate
- Progression to more severe disease due to multi-tissue/organ dysfunction
  - Endothelial dysfunction, systemic coagulopathy and complement-induced thrombosis with development of systemic microangiopathy and thromboembolism
- **Host tissue and organ targets:** lung epithelium, vascular endothelium, brain, kidney, gut, heart, and eye (among others)
- **Therapeutic interventions targeting host-tissue responses are a critical complement to direct anti-virals and passive immune strategies**
Progressive COVID-19 characterized by severe inflammatory response, hypoxia, multi-tissue/organ injury due to direct and indirect viral mediated effects; high endothelial cell expression of ACE2

- Vascular endotheliopathy and prothrombotic/coagulant state with high rates of thrombotic complications

- Poor prognosis consistently associated with dysregulation of:
  - **Renin-angiotensin-aldosterone system (RAAS)** leading to oxidative stress, vasoconstriction, endothelial dysfunction, release of P-selectin, and vWF activation
  - **Immune response** activating complement, neutrophil extracellular traps, and mitogen activated protein kinase pathways
  - **Coagulation cascade, thrombosis, and fibrinolysis** throughout macro- and microvasculature


ACTIV-4 Host Tissue-Directed Therapeutics

Targeting Host-tissue Dysfunction Following SARS-CoV-2 Infection

Target:

**RAAS Dysregulation**
- Inflammation
- Hypoxia
- Fibrosis
- Capillary Leak

**Vascular Immuno-Thrombo-Inflammation Response**
- Hyper-Coagulation
- Pro-coagulant state
- Hypo-fibrinolysis

**Endothelial junction**
- Ang II
- Kal-Brad
- MAC

**Syk**
- Activated macrophage
- Activated neutrophil

**Hyper cytokinaemia**
- NETs

**Endothelial glyocalyx degradation**
- ROS

**Adhesion molecule**
- vWF

**Activated platelet**
- RBCs

**Fibrin**
- Viral antigen

**RAAS Agents (TXA127, TRV027)**

**Fostamatinib**

**Heparin, DOAC, ASA, P2Y12 inhibitors**

Adapted from: Nature Reviews, Nephrology. (17): 46-64, 2021..
NHLBI COVID-19 Clinical Research Framework

**Goals**

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

**COVID-19+ Progression**

- Prevention
- Outpatient Asymptomatic
- Outpatient Symptomatic
- Emergency Department
- Hospital Vent/CPAP-free
- Hospital ICU
- Convalescence
- Recovered

**Host-Directed Therapeutics Clinical Trials**

**Integrated pathobiology/mechanistic studies**

**Screening, Referral and Registries**

**Cohort of Cohorts for Long-Term Follow up**

**Community-Engaged Research Consortium**
"Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies"

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

- Part of NIH ACTIV
- Collaboration with NINDS, other ICs
- Leveraging existing assets, data and studies and forging new partnerships
- Comprehensive, expandable platform linking trial network, registries, mechanistic studies, and cohorts
- Facilitating case finding, clinical trial accrual, longitudinal studies, and community engagement

~300+ sites, ~6,500 ppts in clinical trials, ~58,000 ppts in longitudinal studies
# ENGAGEMENT AND PARTICIPATION OF DIVERSE POPULATIONS

Enriching enrollment of disproportionately affected communities by leveraging community-engagement, multi-disciplinary partnerships across the NIH, and collaboration with patient groups

<table>
<thead>
<tr>
<th></th>
<th>% U.S. Population(^1)</th>
<th>% U.S. COVID Cases(^2)</th>
<th>% Ppts in CONNECTS Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic / Latinx</td>
<td>18.5</td>
<td>27.3</td>
<td>25</td>
</tr>
<tr>
<td>Black</td>
<td>13.4</td>
<td>16.4</td>
<td>22</td>
</tr>
<tr>
<td>Asian</td>
<td>5.9</td>
<td>2.4</td>
<td>3</td>
</tr>
<tr>
<td>Native Hawaiian &amp; Pacific Islander</td>
<td>0.2</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>1.3</td>
<td>1.4</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^1\)United States Census Bureau (2019)  \(^2\)Hollis et al. (2021)
HOST TISSUE-DIRECTED CLINICAL TRIAL PLATFORM STRATEGY

- Collaborating with and leveraging international studies examining same classes of agents:
  - Data integration
  - DSMB collaboration

- Learning system: e.g., strategies to enhance trial start up and completion:
  - 10-fold increase # sites activated and 4-fold increase # participants
  - Reaching more patients through new partners: Outreach through local pharmacies (e.g., CVS)
**ACTIV-4A**: A Phase III Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19

**Patient Population:** Moderately and severely ill hospitalized patients (+/- ventilatory support)

**Interventions/Agents:** Heparin, P2Y12 Inhibitors; (Planned: P-Selectin inhibitor (Crizanlizumab,) SGLT2 Inhibitor)

**Primary Endpoint:** Organ Support Free Days (OSFD)

**Secondary Endpoints:**
- Death, respiratory support, cardiovascular support, renal replacement therapy
- Composite endpoint (discharge or 28 days, whichever occurs first):
  - Death, PE, systemic arterial thromboembolism, MI, ischemic stroke
- Other Secondary Endpoints:
  - Acute kidney injury, 1° & 2°endpoint components, death during hospitalization, WHO clinical scale, 90-day mortality

**Does targeting the pro-thrombotic/pro-coagulant state and endotheliopathy of COVID-19 improve clinical outcomes for hospitalized patients?**
ACTIV-4A: A Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of Antithrombotic and Additional Strategies in Hospitalized Adults with COVID-19

Intervention: Prophylactic or therapeutic dose Heparin

Therapeutic-dose anticoagulation improved survival without need for organ support in moderately ill (non-critical) hospitalized patients but not in critically ill patients.
Demonstrated that platelet-derived factors promote an inflammatory hypercoagulable phenotype, and are significant contributors to poor clinical outcomes in COVID-19 patients.

Testing anti-platelet agents.
**ACTIV-4HT**: A Phase III Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of RAAS and other HT-directed Agents in Hospitalized Adults with COVID-19

**Patient Population**: Moderately and severely ill adult hospitalized patients treated with oxygen for hypoxemia

**Interventions/Agents (Arms)**:
- Renin-Angiotensin-Aldosterone System (RAAS) Agents:
  - TXA127 and TRV027
  - Inhibition of vascular inflammation:
    - Fostamatinib (spleen tyrosine kinase (SYK) inhibitor)
  - Placebo

**Target enrollment**: 300 per arm

**Primary Endpoint**: Oxygen-free days from randomization through 28d

**Secondary Endpoint**: Mortality, WHO 8-point ordinal scale, support-free days through 28d

Can RAAS-targeting agents and/or Fostamatinib prevent COVID-19 host-tissue responses: vascular injury, inflammation, fibrosis, capillary leakage, and thrombosis?

**ACTIV-4HT**: A Phase III Multicenter, Adaptive, Randomized Controlled Platform Trial of the Safety and Efficacy of RAAS and other HT-directed Agents in Hospitalized Adults with COVID-19

**Builds upon Phase II NHLBI study:**

**Phase II Trial of Fostamatinib:**
Safe in hospitalized patients requiring oxygen and associated w/ trend to clinical and biochemical improvement (esp. in severely ill patients)

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Outpatient Asymptomatic</th>
<th>Outpatient Symptomatic</th>
<th>Emergency Department</th>
<th>Hospital Vent/CPAP-free</th>
<th>Hospital ICU</th>
<th>Convalescence</th>
<th>Recovered</th>
</tr>
</thead>
</table>

**Clinically Stable Symptomatic Outpatients**

**POPULATION**
- 388 Women
- 269 Men

Outpatients with symptomatic COVID-19, platelet count \(>100,000/\text{mm}^3\), and estimated glomerular filtration rate \(>30\ \text{mL/min}/1.73\text{m}^2\)

Median age: 54 years

**LOCATIONS**
- 52 Sites in the US

**INTERVENTION**
- 657 Patients randomized
- 558 Patients analyzed

- 164 Aspirin 81 mg/d + matching placebo for 45 days
- 165 Prophylactic apixaban 2.5 mg twice/d for 45 days
- 164 Therapeutic apixaban 5 mg twice/d for 45 days
- 164 Placebo Placebo twice/d for 45 days

**PRIMARY OUTCOME**
Composite of all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause

**JAMA Original Investigation**
Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19
The ACTIV-4B Randomized Clinical Trial

JAMA November 2, 2021 Volume 326, Number 17

**Anti-thrombotic prophylaxis (ASA, DOAC) is not indicated to reduce adverse cardiopulmonary outcomes in symptomatic but clinically stable COVID-19 outpatients**
**ACTIV-4C**: A Phase III Multicenter, Adaptive, Randomized Platform Trial Evaluating the Safety and Efficacy of Antithrombotic strategies in COVID-19 Patients Following Hospital Discharge

**Intervention/Agent**: Apixaban

**Patient Population**: Enrolling adults > 18 years of age with COVID-19 who are hospitalized > 48 hours and ready for discharge

**Primary Endpoint**: Thrombotic Event; Binary composite endpoint of venous and arterial thrombotic complications and all-cause mortality

**Secondary Endpoint**: Individual outcomes of the composite primary endpoint, the time-to-event for the composite primary endpoint, and a clinical rank-based score

**Clinicaltrials.gov**: https://clinicaltrials.gov/ct2/show/NCT04650087

**Can anti-thrombotic therapy in the post-acute setting prevent thrombo-embolic events and improve survival after hospital discharge?**
Development of Host Tissue-Directed Therapeutics: Vital to Future Pandemic Preparedness

1. **Initial phase of a viral pandemic**: specific anti-viral agents (i.e. vaccines, anti-virals, or monoclonals) not readily available

2. **Later phases**: Even in presence of specific antiviral reagents, delays in effective protection to all components of the population

3. **Subsequent phase of a viral pandemic**: Pathogen evolves, is able to evade specific antigen recognition upon which vaccine and passive immunization strategies rely, and/or is able to circumvent mechanisms of, for example, specific protease inhibitors

4. **Post-acute infection phase** may be associated with significant host tissue sequelae which will require monitoring and development of therapeutic and prophylactic interventions

Thank you to Patients, Researchers, NIH and HHS Staff, for your critical role in improving COVID-19 therapies.