NIH ACTIV: Rapidly Advancing Understanding, Prevention, and Treatment of COVID-19-Associated Coagulopathy (CAC)

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COVID-19 Has Severe Effects on the Lung, Heart, Vascular and Blood Coagulation Systems

What We Know About COVID-19-Associated Coagulopathy (CAC)

- Blood clots in many critically ill patients
- 71% of COVID-19 patients who died in China had systemic coagulopathy
- Wide range of affected patients
- Causing pulmonary embolism, myocardial infarction, stroke, deep-vein thrombosis
- Unclear if young people have > CAC rate
- Increased levels of D-dimer* strongly associated with increased mortality
- Microvascular thrombosis (arterial/venous)
- Compromised oxygenation and multi-organ failure

Currently no clear standard-of-care for anticoagulation in hospitalized COVID-19 patients

Urgent need for clinical evidence to guide practice

*biomarker elevated in conditions associated with thrombosis
Understanding, Preventing, and Treating COVID-19 Coagulopathy (CAC): A Collective Path Forward

Identifying the Mechanism: What is/are the clotting trigger(s) from COVID-19 viral infection (e.g. endothelial dysfunction/injury, inflammatory response)?

Understanding Disease Severity: What is the role of thrombosis in lung dysfunction, organ failure?

Generating Evidence to Guide Clinical Care: What is the best treatment of coagulopathy in COVID-19 patients at different stages of illness?

COVID-19+ Progression

Prevention → Outpatient Asymptomatic → Outpatient Symptomatic → Emergency Department → Hospital Vent/CPAP-free → Hospital ICU → Convalescence → Recovered
ACTIV Public-Private Partnership: An Integrative Strategy to Advance COVID-19 Therapeutics

ACTIV Public-Private Partnership
Accelerating COVID-19 Therapeutic Interventions & Vaccines

Working groups

Preclinical
- Increase access to animal models
- Identify informative assays

Therapeutics clinical
- Prioritize and test potential therapeutic agents
- Develop master protocol for clinical trials

Clinical trial capacity
- Develop survey instruments
- Develop inventory of clinical trial networks
- Guide deployment of innovative solutions

Vaccines
- Accelerate evaluation of vaccine candidates
- Identify biomarkers to speed approval
- Provide evidence to address safety concerns

Federal Partners

Non-Profit Partners
- Foundation for the National Institutes of Health
- Bill & Melinda Gates Foundation
- Fred Hutchinson Cancer Research Center
- RTI International

Bio/Pharma Industry Partners
- AbbVie
- Amgen
- AstraZeneca
- Bristol Myers Squibb
- Evotec
- GlaxoSmithKline
- Johnson & Johnson
- KSQ Therapeutics
- Eli Lilly and Company
- Merck & Co., Inc.
- Novartis
- Pfizer
- Roche
- Sanofi
- Takeda
- Vir Biotechnology

ACTIV-4 : PROTECT-COVID 19

ACTIV PPP leverages trans-NIH clinical trial capacity for adaptive clinical trial designs with Master Protocols and conducts cross-disciplinary research with biorepositories for leading-edge natural history studies.

- **Leverage networks’ expertise and efficiency**
  - Enhance recruitment speed; facilitate specialized sub-studies

- **Maximize knowledge: Sampling, Imaging, Analysis**
  - Risk stratification; clinical phenotyping
  - Stroke and blood-brain barrier
    - Imaging capacities for blood-brain barrier impairment at selected site(s)
  - Interface between inflammation and coagulation
    - Innate immune response
    - Adaptive immune response
Randomized Trial of Anti-Thrombotic Strategies in COVID-19 (PROTECT-COVID 19)

- First open-label trial to compare blood-clotting regimens in COVID-19 + patients
- Phase III clinical trial with focus on low and high doses of heparin
- Evolving as an adaptive platform clinical trial to study other anticoagulants, antiplatelet agents
- Studies will identify biomarkers to enable patient risk stratification

- 1,000 COVID-19 + patients, starting in NY & approximately 15 additional sites
- Includes hospitalized patients with a D-dimer >500 ng/ml
- Patients randomized to higher-dose versus lower-dose heparin in 1:1 ratio.

Antithrombotic: Prophylaxis and Treatment
ACTIV Public-Private Partnership: A Rapid Response to Reduce COVID-19 Morbidity and Mortality

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