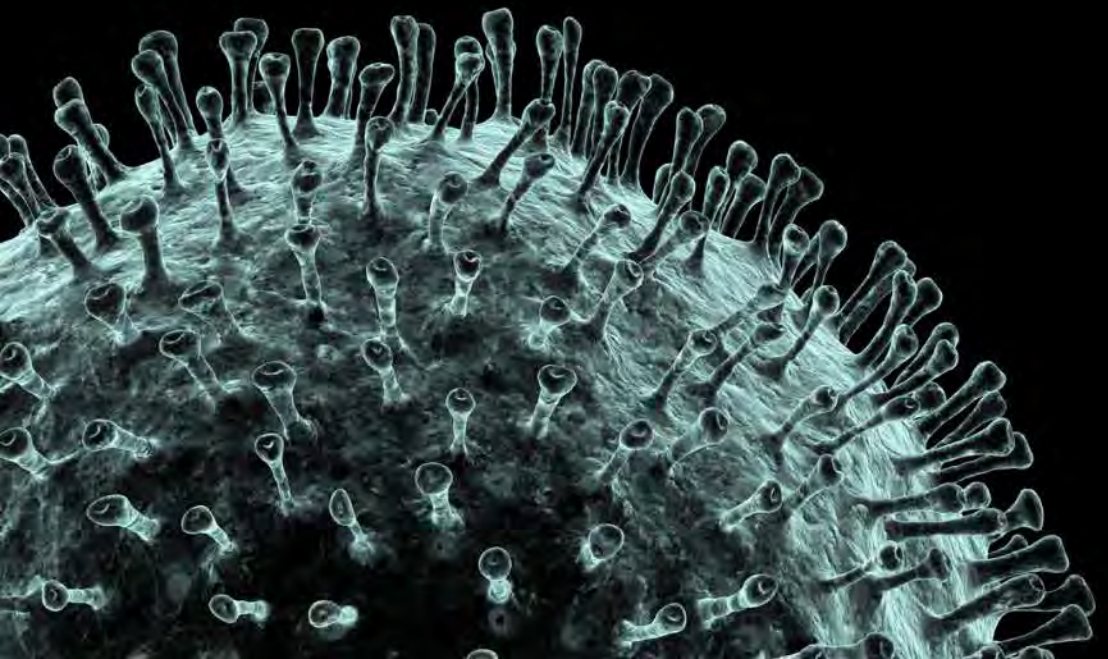
COVID-19 Conversations

Judith Currier

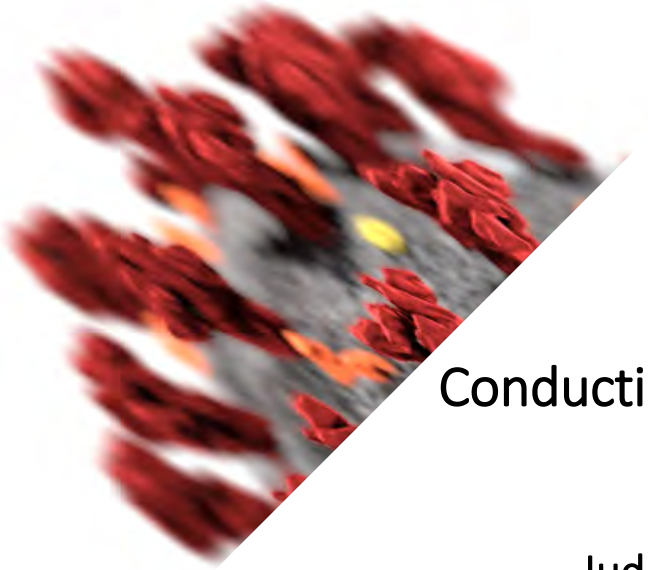
Professor of Medicine, UCLA Division of Infectious Diseases
Division Chief, Infectious Diseases



COVID19Conversations.org
#COVID19Conversations

APHA
AMERICAN PUBLIC HEALTH ASSOCIATION
For science. For action. For health.

50 years
NATIONAL ACADEMY of MEDICINE



Conducting Clinical Trials during a Pandemic

Judith S. Currier, MD, MSc
Professor of Medicine
Chief, Division of Infectious Diseases
Michael and Sue Steinberg Chair in Global AIDS Research
David Geffen School of Medicine, UCLA
Chair, AIDS Clinical Trials Group

Setting the Stage

- Global Pandemic
- High mortality rate for patients admitted to hospital
- No known treatment, limited understanding of how to manage the disease initially
- Highly transmissible infection
- Many potential therapies to evaluate, including “re-purposed drugs” already approved for other diseases and drugs that appear effective in the test-tube
- Need to figure out which treatments are effective and safe as fast as possible

Topics

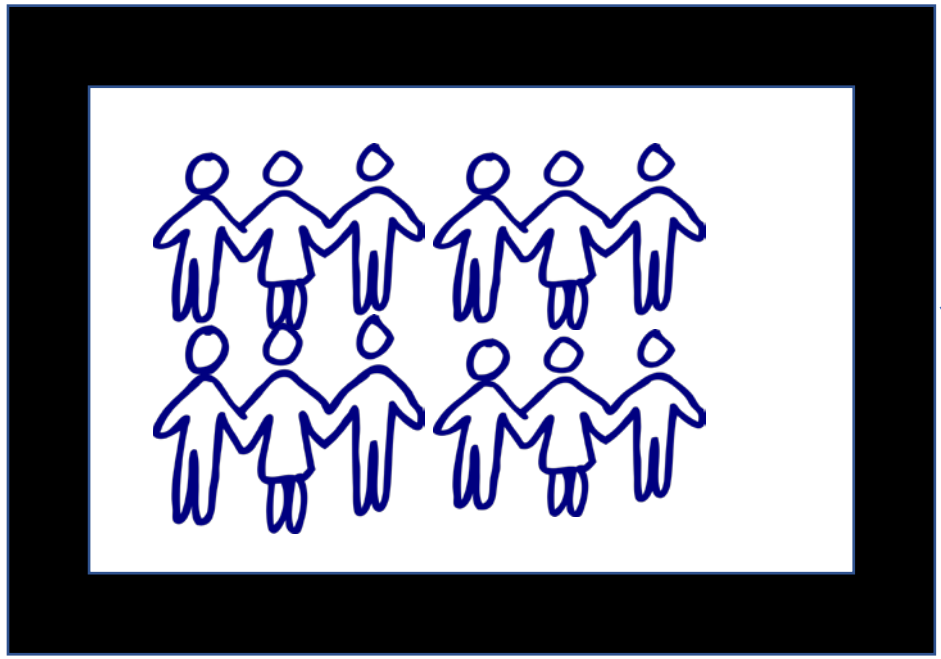
Randomized clinical trials- what are they and why do we need them to learn how to treat COVID-19?

Implementation challenges

Lessons Learned from COVID-19

Randomized Clinical Trials

design → conduct → analyze data



Eligible Participants

Randomized

Experimental Treatment

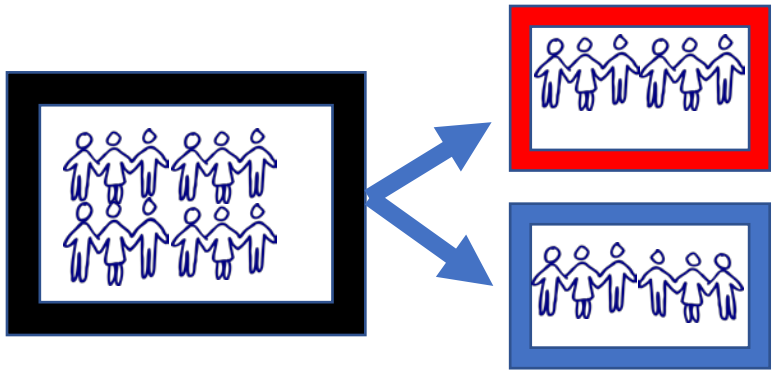
Placebo/Standard of Care Treatment

Compare Outcomes

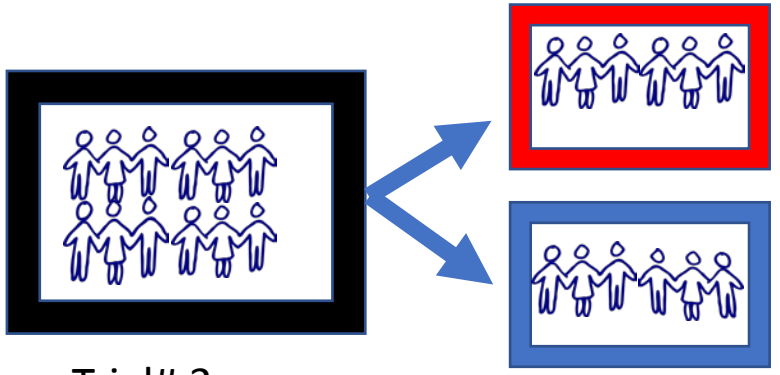
Strength of Randomized Trials vs Other Approaches

- Randomly assigns people to treatment group
  - Compare groups that are balanced for characteristics that could impact outcome
  - During a new disease we don't yet know which factors could impact outcome (age, sex, co-morbidities)
- When active treatment and control and "blinded" provides unbiased assessment of outcomes, including safety events
- Observational studies add value, but cannot replace randomized trials, especially with a new disease where the natural history is undefined
  - Sicker patients more likely to be offered treatment and it is not possible to control for confounders when you don't know what they are

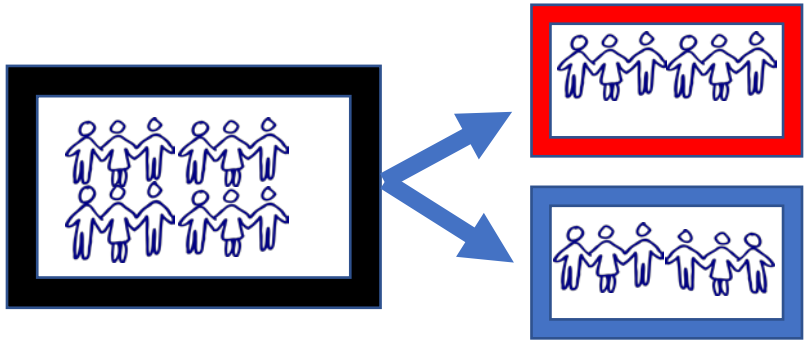
What if we want to study multiple new agents quickly
Do they all need their own placebo? Can we do this more efficiently?



Trial #1

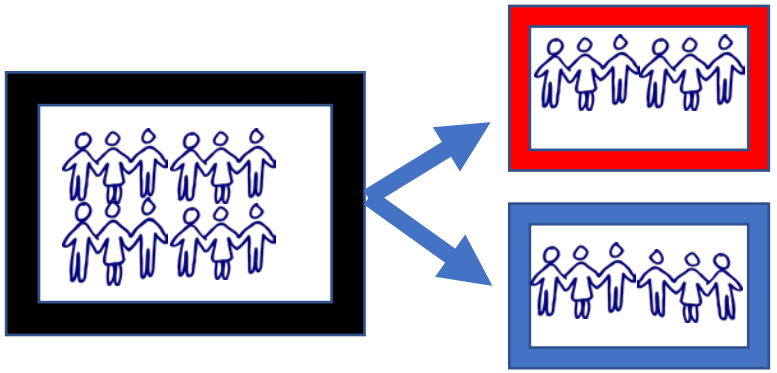


Trial# 3



Trial # 2

Trial # 237



Adaptive Platform Trials to the Rescue

Adaptive Platform Trials Coalition
Nature Reviews
October 2019

PERSPECTIVES

OPINION

Adaptive platform trials: definition, design, conduct and reporting considerations

The Adaptive Platform Trials Coalition

For example, APTs require considerable pretrial evaluation through simulation to assess the consequences of patient selection and stratification, organization of study arms, within-trial adaptations, overarching statistical modelling and miscellaneous issues such as modelling for drift in the standard of care used as a control over time. In addition, once APTs are operational, transparent reporting of APT results requires accommodation for the fact that estimates of

- APT is a trial of alternative treatment strategies.

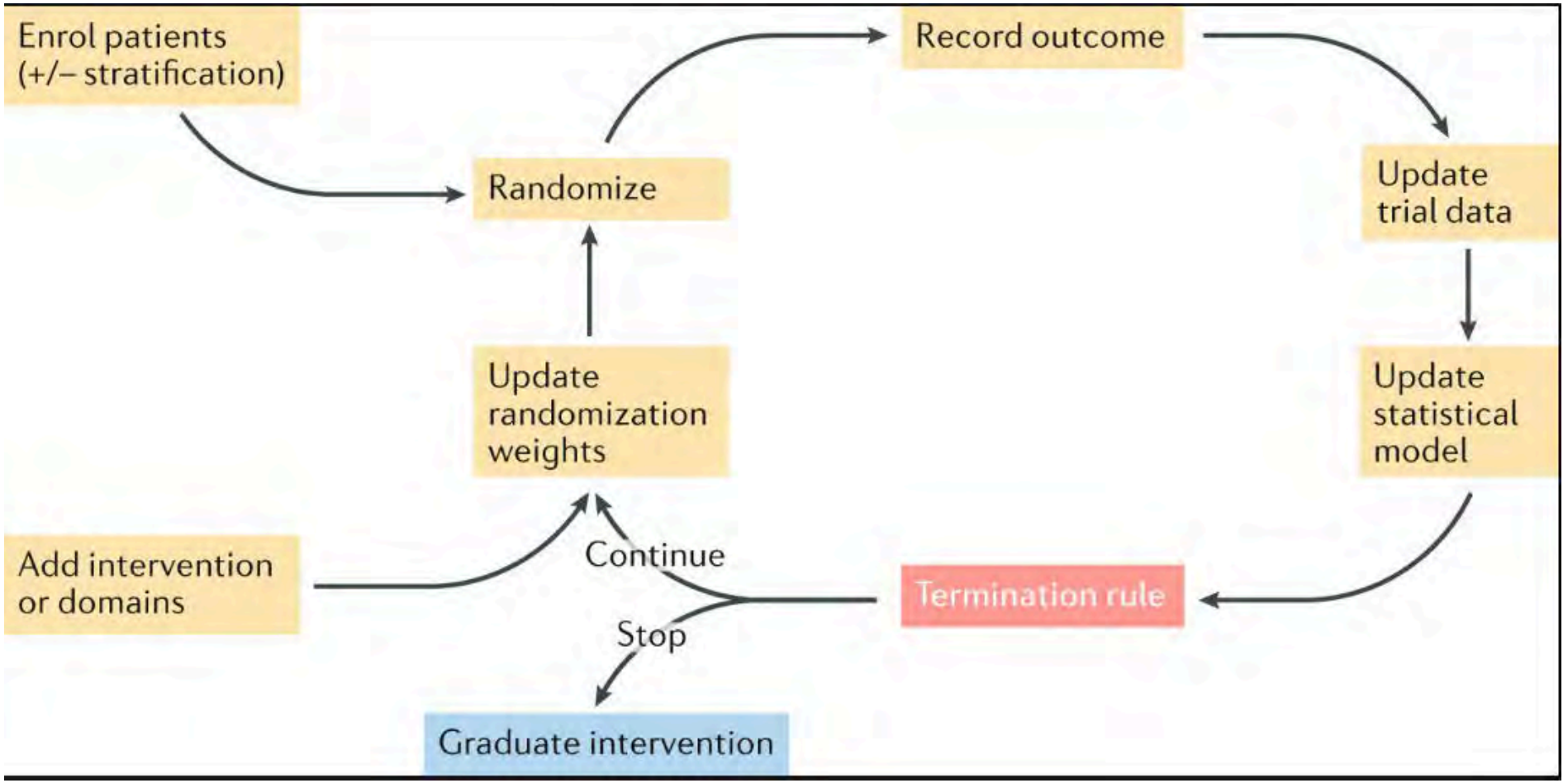
- A platform with a master protocol,
- upon which multiple questions can be asked about
- the effectiveness of interventions for a disease.

- Information generated during trial conduct
- can alter subsequent operations in a pre- specified
- way “adaptive”.

- Allows the placebo arm to be “shared” across treatment arms, yielding results sooner than traditional trial
- Trial can adapt to new information learned about the disease during conduct, agents that perform poorly can be dropped, new ones can be added
- Used during Ebola Outbreak and now several examples of Adaptive Platform Trials for COVID-19 → RECOVERY, ISPY-2, REMAP-CAP COVID and soon ACTIV 2, ACTIV 3

Adaptive Platform Trial Design for COVID-19

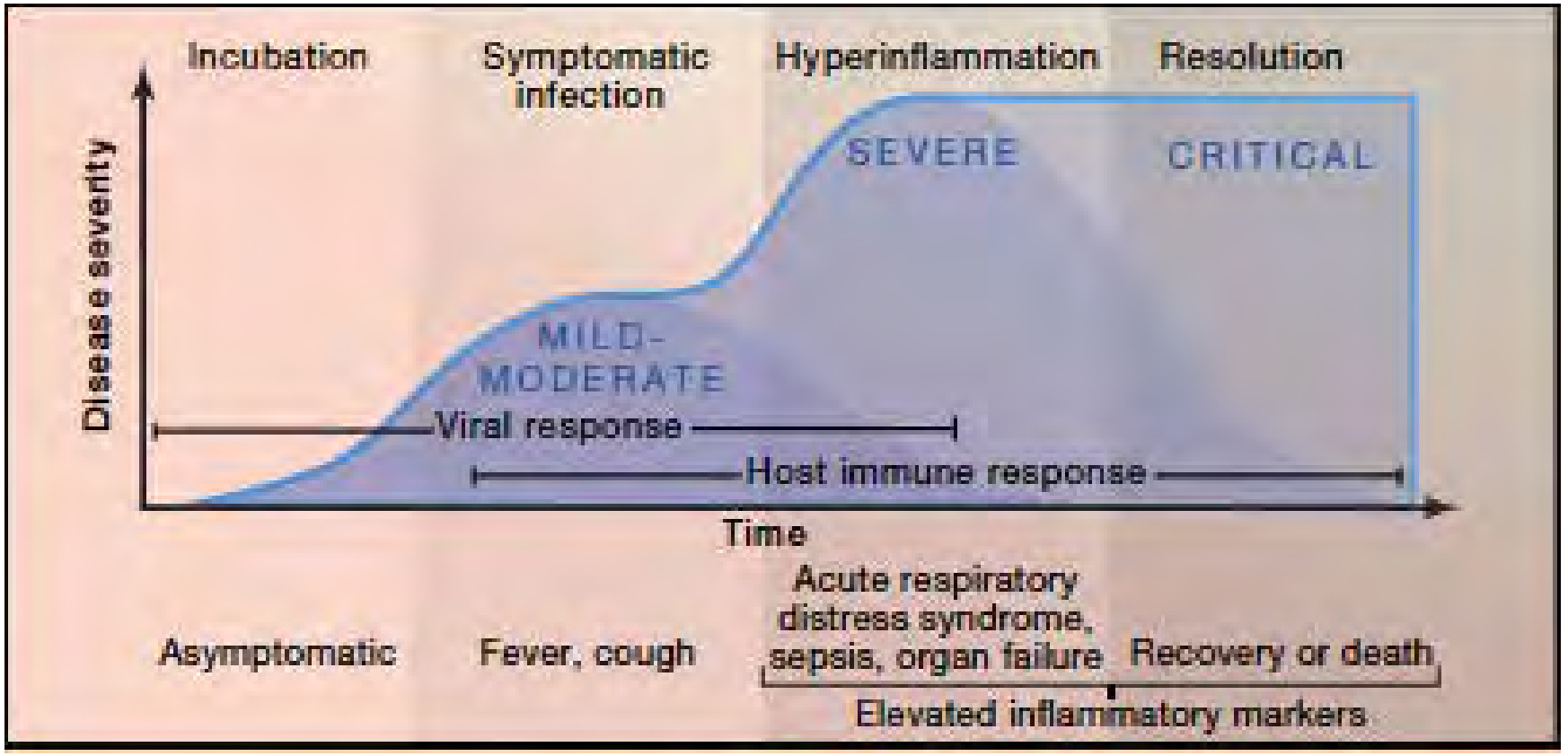
Treatments



Successful Treatment Becomes New Control Group

Adapted from Angus, D.C., Alexander, B.M., Berry, S. *et al. Nat Rev Drug Discov* **18,** 797–807 (2019).

Efficacy of interventions and safety may vary across the time course of disease
Need to study treatments at different stages of disease



Adapted from Cell https://doi.org/10.1016/j.cell.2020.04.013

Implementation Challenges
Hospitalized Patients- severe disease

- Standards of supportive care rapidly evolve as we learn to treat the disease
- Patients are in isolation rooms in hospital
  - No visitors= no family at bedside
  - Limited entry to room, blood draws extra testing
- Remote informed consent via zoom, telephone, with patient or legal authorized representative
- Systems working at capacity during surge, personnel to conduct trials limited, stretched
- Limitations in supplies- PPE, nasal swabs for measuring viral shedding
- Disparities in location of trials
  - Some hospitals have numerous trials competing for patients
  - Others have no access to trials due to lack of infrastructure

Implementation Challenges
Outpatients- mild disease

- People are in quarantine, not able or willing to come to a site for a trial
  - Novel approaches →Remote enrollment online, remote informed consent, shipping study treatment and collecting self reported outcomes
  - Feasible, but loss to follow-up may be higher, Biologic outcomes harder to confirm
  - Maybe ideal for certain types of interventions, less so for experimental therapies with unknown safety profiles
- Adaptive clinical trial locations
  - Tents
  - POD Structures configured as isolation units
  - Mobile vans

Implementation Challenges

- Studies need to be able to enroll populations reflective of those who are experiencing the disease
- Pregnant women and Children – limited inclusion in most interventional COVID-19 trials to date
  - Bridging Trials and Compassionate Use programs
  - Collection of data from all sources
- **Coordination across Industry, Government, Academia, Foundations**

On April 17, NIH announced the launch of a public-private partnership, **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV),** to develop a **coordinated research response to speed COVID-19 treatment and vaccine options.**

- Establishing a **collaborative framework for prioritizing therapeutic candidates and accelerating vaccine evaluation**
- **Accelerating clinical trials of promising agents and leveraging existing clinical trial networks while maintaining rigorous safety standards**
- **Coordinating regulatory processes and leveraging assets among all partners**

Collins FS, Stoffels P. Accelerating COVID-19 Therapeutic Interventions a
Vaccines (ACTIV): An Unprecedented Partnership for Unprecedented
Times. *JAMA.* Published online May 18, 2020. doi:10.1001/jama.2020.89

Coordinated by the Foundation for the National Institutes of Health (FNIH), **ACTIV brings together multiple partners from government, industry, and non-profits:**

7 Government Partners

BARDA
CDC
DoD
EMA
FDA
NIH
VA

18 Industry Partners

AbbVie
Amgen
AstraZeneca
Bristol Myers Squibb
Eisai
Eli Lilly and Company
Evotec
Gilead
GlaxoSmithKline
Johnson & Johnson
KSQ Therapeutics
Merck
Novartis
Pfizer
Roche-Genentech
Sanofi
Takeda
Vir Biotechnology

3 Nonprofits

Bill & Melinda Gates Foundation
Fred Hutchinson Cancer Research Center
RTI International

Lessons we are learning during COVID-19

- Dedicated infrastructure for clinical trials at sites, trained investigators speed implementation
  - Rapid deployment of successful trials was facilitated by infrastructure built over past 30 years of clinical research investments for other diseases
  - Disparities in the location of these resources magnified by COVID-19
- Adaptive Platform Trials with well defined outcomes and the ability to compare multiple strategies and to learn as we go are yielding important results
- Necessity is the Mother of Invention
  - Remote monitoring of participants during follow-up
  - Simplified trials
  - Tremendous collaboration and coordination between groups

Host: Risk Factors for Severe COVID-19 in Adults

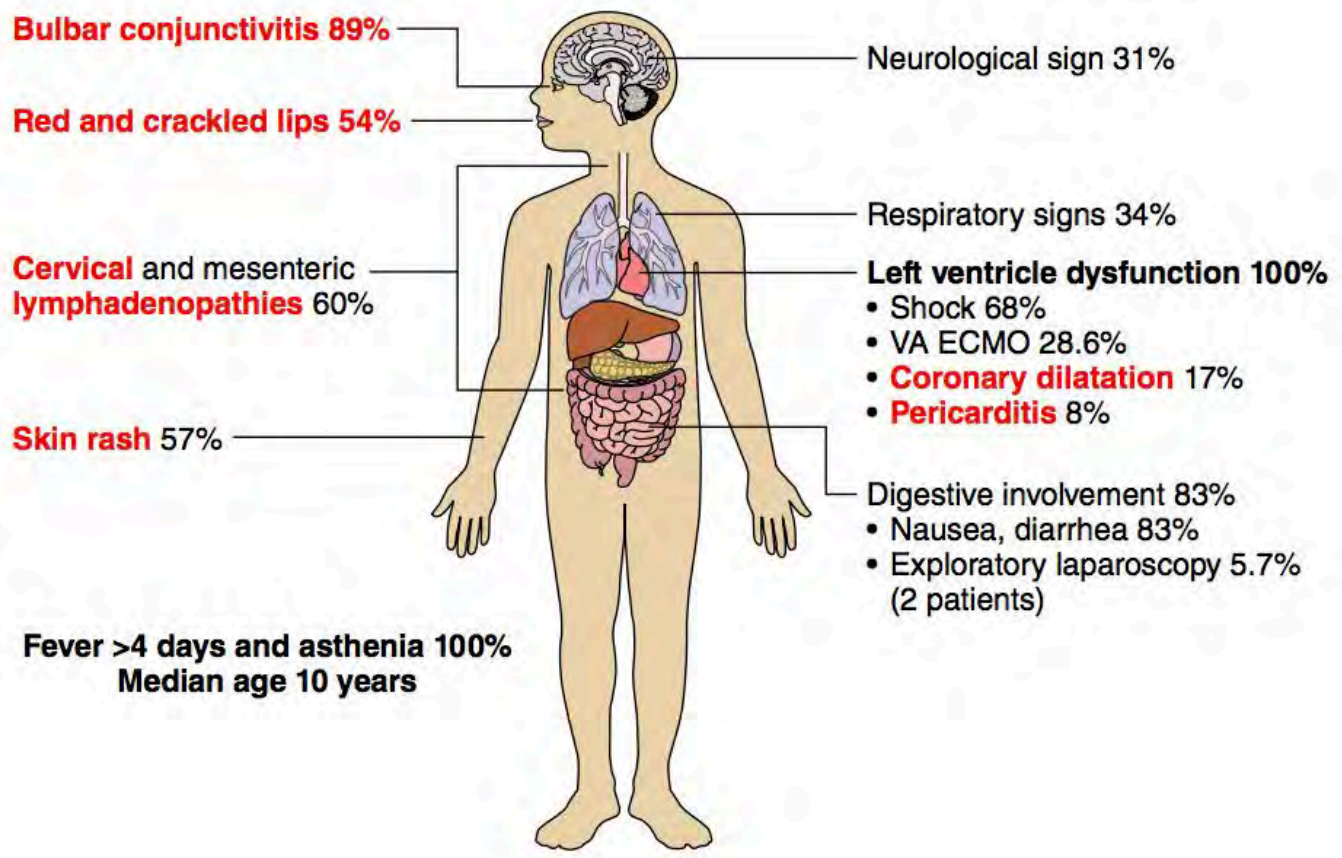
Table 1. Established and Potential Risk Factors for Severe Covid-19.*
Older age (e.g., >65 years)
Chronic lung disease
Cardiovascular disease
Diabetes mellitus
Obesity
Immunocompromise†
End-stage renal disease
Liver disease

- Immunosuppression, including advanced HIV (CD4 cell count <200), is risk factor for complications of other respiratory viruses. Not known if people with HIV are at increased risk for severe COVID-19.
- Disproportionate burden of COVID-19 among racial and ethnic minorities, Native Americans

Gandhi RT, Lynch JB, del Rio C, NEJM 2020

Host: Multisystem Inflammatory Syndrome in Children

- Acute vasculitis with some similarities to Kawasaki disease
- Fever, rash, conjunctivitis, abdominal pain, shock and cardiac dysfunction
- Children may have had recent SARS CoV-2 infection – MIS-C may represent a post-infectious hyper-inflammatory syndrome



Belhadjer Circulation 2020 https://doi.org/10.1161/CIRCULATIONAHA.120.048360;
Jones Hospital Peds 2020 https://doi.org/10.1542/hpeds.2020-0123
Verdoni Lancet 2020 https://doi.org/10.1016/S0140-6736(20)31103-X

Multidimensional Challenge of Treating COVID-19

Host	• Adults • Children • Risk factors for severe disease
Stage and Severity	• Early vs. late infection • Mild, moderate, severe, critical disease
Intervention	• Antivirals • Immunomodulators • Combination therapy • Rx complications: anticoagulation, ventilation